

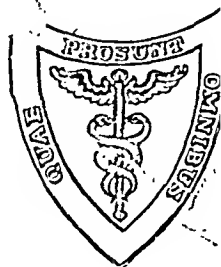
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RICHARD A. KERN, M.D.
ASSISTANT EDITOR

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THE
AMERICAN JOURNAL
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JANUARY, 1942

ORIGINAL ARTICLES.

THE VASCULAR AND CELLULAR DYNAMICS OF SHOCK.*

By VIRGIL H. MOON, M.D.,

PROFESSOR OF PATHOLOGY, THE JEFFERSON MEDICAL COLLEGE AND HOSPITAL,
PHILADELPHIA, PA.

THE phenomena of shock have both fascinated and baffled physicians for more than a century. Few conditions of disease have been subjected to more diversified or more penetrating investigations than this, yet final clarification has been delayed. We shall not review the attempts to solve this enigma nor summarize the resulting contributions of factual evidence. Rather, we shall inquire why diligent efforts have led to divergent interpretations. An analysis of the causes for disagreement may be more illuminating than a reëxamination of the existing data.

Shock has been our chief interest for many years, during which we have retraced many trails left by our predecessors and have made several excursions into regions not hitherto explored. More than 400 animals have been used in experiments on various phases of the problem, and the antemortem features of shock have been compared with the necropsy findings in more than 100 clinical cases. This statement merely indicates that the material studied was adequate in amount. Out of these experiences has grown the conviction that the conflicting interpretations of shock have originated from four major sources. Attention is invited successively to each of these causes for confusion.

Circulatory Failure of Capillary Origin. Deficiency of knowledge concerning the functions and reactions of capillary endothelium was the first major hindrance to a comprehension of shock. A clearer understanding of capillary physiology (Krogh¹⁷), and of the related mechanisms of water balance and cell permeability, has removed

* This paper was prepared by request of the Council of the American Association of Pathologists and Bacteriologists for presentation at their Annual Session, April 11, 1941.

this hindrance and has illuminated many processes which formerly were obscure. A brief reference to capillary reactions is essential to the discussions which follow.

Each organ and tissue has a supply of capillaries adequate to its maximal circulatory needs. In resting or inactive tissues most of these are contracted and bloodless, while in functioning tissue they are hyperemic. Barcroft² showed that muscles during activity require 20 to 40 times more blood than when at rest. Functioning cells consume oxygen and liberate products of metabolism and since capillary endothelium is delicately susceptible to lack of oxygen, the walls relax and the endothelium becomes more permeable whenever moderate anoxia develops. This relaxation allows an increased flow of arterial blood, supplying oxygen and other nutrients. Fresh arterial blood contains a hormonal substance, perhaps of pituitary origin, which causes the capillaries again to contract. This limits the flow of blood until lack of oxygen and/or the accumulation of metabolites again causes relaxation. Thus the local circulatory cycle is repeated at a rate commensurate with the functional activity of the cells.

Endothelium, which is very sensitive to anoxia and to metabolites, is highly susceptible to other agents also. Heidenhain,¹⁴ some 50 years ago, discovered that peptone will produce a decline in blood pressure accompanied by an increased flow of lymph when given intravenously to dogs. He found that extracts of various marine animals and of normal tissues, as liver, pancreas, mucosa, muscle and others, produced the same effects. He noted that both the volume and the protein content of the lymph were increased while total solids of the blood were increased and its plasma volume was decreased. The latter change is now designated by the term *hemoconcentration*. He stated that these effects are characteristic of the action of these "lymphagogues" and attributed them to increased secretory activity of the endothelium.

After the lapse of half a century, increased knowledge of capillary physiology has revealed the full significance of Heidenhain's observations. The increased flow of lymph, its high protein content, the declining blood pressure, the decreased plasma volume and the hemoconcentration, result from the leakage of plasma through endothelium rendered abnormally permeable by the effects of the agents used. Many other substances have been shown to produce the same effects. These include certain alkaloids, diphtheria toxin, tuberculin and other bacterial products, foreign proteins and products of protein cleavage, histamine, bile and cholic salts, venoms and many drugs, chemicals and poisons. These agents have been called capillary poisons for they have one property in common—that of producing relaxation and increased permeability of capillary endothelium.

These reactions illuminate a type of circulatory disturbance

which hitherto was imperfectly understood. The effects described tend to create a disparity between the volume of blood and the volume capacity of the vascular bed. Dilatation of the capillaries and venules *increases the volume capacity*, while leakage of plasma through the capillary wall *lowers the total blood volume*. This disparity, if marked, impairs the systemic circulation and produces characteristic morphologic changes in the viscera. The latter consist of dilatation and engorgement of capillaries and venules, petechial hemorrhages resulting from endothelial dissolution, stasis as shown by compact masses of corpuscles in the minute vessels, edema of soft tissues and acute granular degeneration, often accompanied by focal necroses, in parenchymatous organs.

Incipient disparity between the volume of blood and the volume capacity of the vascular bed is compensated for by physiologic reactions. Impulses, probably originating in the carotid sinus, activate the sympatho-adrenal system. The systemic action of adrenalin stimulates the myocardium, mobilizes glucose from the liver, contracts the peripheral arteries, and causes the discharge of reserve blood from the spleen and other reservoirs. So long as this compensation is adequate, there is no ominous decline in the arterial blood pressure, but the latter is maintained at the expense of volume flow. When finally the mechanism of compensation becomes inadequate, the blood pressure declines progressively and the circulatory deficiency is manifested clinically.

Clinical Features. Prostration is evident; the patient is profoundly depressed, weak and restless. The pulse is rapid, feeble and of small volume. The extremities are cold and the body temperature is low. The face is drawn, ashen or livid in color, anxious in expression, and moist with cold sweat. The eyes are sunken and surrounded by bluish rings, producing the classical "Hippocratic facies." Thirst is incessant, but attempts to relieve it are ineffective because of vomiting. The fluid vomited is often in excess of that swallowed and it usually contains small brown flocculi. Perspiration is profuse, and there may be diarrhea. The respirations are shallow and interspersed with deep sighs. Urination is scanty or suppressed. The blood pressure declines progressively. Consciousness is retained until finally there is loss of sensitivity, of responsiveness to stimuli and of reflexes. Unconsciousness or coma precedes death.

The clinical syndrome just described is accompanied by an equally characteristic group of departures from physiologic constants. These are: a reduced total and effective blood volume; a reduced minute volume cardiac output and volume flow of arterial blood; hemoconcentration, increased non-protein nitrogen, glucose and potassium content of the blood; reduced metabolism, alkaline reserve, chloride and oxygen content, and delayed coagulability of the blood. An increased flow of lymph from the thoracic duct is

an early and constant feature when this condition is produced experimentally.

Fluid Balance. Hemococoncentration, which means an increase in the ratio of erythrocytes to plasma per unit volume of blood, is a highly significant feature in the pathologic physiology of shock. Sherrington,²⁸ Crile,⁶ Henderson¹⁵ and other early investigators noted this phenomenon in experimental shock; Cobbett,⁵ King¹⁶ and Vale²⁰ recorded its occurrence in surgical shock. During the previous World War it was found that hemoconcentration was the earliest detectable sign of shock in wounded soldiers (Cannon⁴). The erythrocytic counts ranged from about 6,000,000 in mild cases to over 9,000,000 in severe shock. These cases were differentiated from the effects of hemorrhage by the *dilution* of blood resulting from the latter. A survey of the recorded observations^{21d} indicates that the blood regularly becomes concentrated as circulatory failure of capillary origin develops. This results from loss of plasma volume incident to leakage of fluid into the tissue spaces, due to abnormal permeability of the endothelium. It is integrally related to the increased flow of lymph discussed previously and also to the development of edema. It appears that these phenomena occur whenever and however the endothelium in an extensive visceral area is damaged.

Any type of injury to endothelium renders it abnormally permeable to plasma, and, if extensive, it deranges seriously the mechanism of water balance and of absorption. The movement of fluid between the blood and the tissues depends upon the action of several factors, including capillary blood pressure, osmotic pressures, electrolytic concentrations, hormonal substances and others. *But the presence of a normal semipermeable membrane, the endothelium, is absolutely essential to the action of these forces in preserving a physiologic relationship between intravascular and extravascular fluids.* So long as the endothelium is able to perform its part in the maintenance of fluid balance, no hemoconcentration occurs. A change in the permeability of the endothelium deranges the processes by which both blood volume and concentration are maintained at physiologic levels. A significant increase in the concentration of the blood is of grave importance for it indicates a derangement in the vital mechanism of water balance.

Increased Cellular Permeability. This plays a rôle in the pathologic physiology of shock, not less significant than endothelial permeability. Students of cell physiology (Lucké and McCutcheon's¹⁹ review) have shown that the outer protoplasmic surface of each living cell functions as a semipermeable membrane and that, by virtue of this, each cell behaves as an osmotic unit. Some property possessed by living protoplasm maintains chemical concentrations within the cell, differing markedly from those of the external fluid (Gamble¹⁷). Some of these are shown in Diagram 1:

NORMAL.

Cellular fluid	Extra-cellular fluid
$\left. \begin{array}{l} \text{K, Mg, Ca} \\ -\text{HPO}_4, -\text{SO}_4 \\ \text{Na, -Cl, -HCO}_3 \end{array} \right\}$	$\left. \begin{array}{l} \text{K, Mg, Ca} \\ -\text{HPO}_4, -\text{SO}_4 \\ \text{Na, -Cl, -HCO}_3 \end{array} \right\}$
>	<

INJURY TO CELLS.

Cellular	RESULT.	Extra-cellular
$\left. \begin{array}{l} \text{K, Mg, Ca, Na} \\ -\text{HPO}_4, -\text{SO}_4 \\ -\text{Cl, -HCO}_3 \end{array} \right\}$	=	$\left. \begin{array}{l} \text{K, Mg, Ca, Na} \\ -\text{HPO}_4, -\text{SO}_4 \\ -\text{Cl, -HCO}_3 \end{array} \right\}$

DIAGRAM 1.—The ability to maintain normal differences in concentrations is reduced by any kind of cellular injury and is lost entirely as the cell dies. This allows electrolytes to pass freely from the region of the higher concentration to that of the lower, thus tending to equalize the differences in composition.

For example, the cellular and extracellular fluids differ widely in their normal content of potassium, the approximate degree of which is shown in the following ratio:

$$\text{K (Cellular)} : \text{K (Extra-cellular)} = 21:1$$

The extracellular fluids have been estimated as 15% of the body weight. A simple computation, on the basis of these figures, indicates that complete equalization in the ionic concentrations would result in raising the potassium content of the extravascular fluids to approximately 18 times its normal level. None of the published data, on chemical alterations in the blood during shock, have shown such a high potassium content as this. It is evident that this maximal level could only be reached by *complete* equalization of the chemical concentrations, which condition probably would occur at or after death. Cellular injury tends to allow equalization in the concentration of other ions as well.

Scudder²⁵ suggested that the high potassium content of the plasma and interstitial fluid *caused* cellular injury and thus was an important etiologic factor. However, his data show that hemoconcentration *precedes* the chemical changes. This indicates that the latter are effects rather than causes.

The same injurious agents, which disturb the fluid balance by affecting the endothelium, may also disturb chemical concentrations by increasing cellular permeability. The former effects result in shock accompanied by hemoconcentration; the latter effect provides a satisfying explanation for the accompanying chemical alterations in the plasma and tissue fluids. The constancy of cellular environment, *physiologic homeostasis* (Cannon⁴), is destroyed and the mechanism for its restoration is vitally deranged. This disturbance of electrolytic balance is scarcely less serious than the associated disturbances of the circulation and of fluid balance.

Few conditions of disease have a more typical clinical picture, more significant physiologic pathology and more characteristic visceral changes than those depicted. They are the clinical and pathologic features which are distinctive of circulatory failure of capillary origin. The term *shock* is commonly used to denote this syndrome. It may be defined in physiologic terms as *a type of circulatory failure, not central but peripheral in origin, characterized by decreased blood*

volume, decreased volume flow and by hemoconcentration. This type of circulatory failure may develop after severe traumatic injury, prolonged or complicated surgical procedures, and after extensive burns of the skin. It occurs also incident to abdominal emergencies such as strangulation, perforations, intestinal infarction, pancreatitis, and it is seen in intoxications, infections of unusual severity, serum disease and in acute poisoning of diverse kinds. The same syndrome may be produced experimentally by trauma, intestinal manipulation, burns and by other forms of tissue abuse in animals or by the injection of various capillary poisons previously referred to.

When this syndrome results from traumatic injury, extensive surgery or tissue abuse, it is usually complicated by hemorrhage and by other factors; but it can be produced in uncomplicated form by various agents which cause endothelial damage. The mechanism of this type of circulatory disturbance may be shown diagrammatically. Most important in that mechanism are the two major factors, *capillary atony* and *anoxia* which, because of their reciprocal effects, give this mechanism the self-perpetuating quality of a vicious circle (Diagram 2).

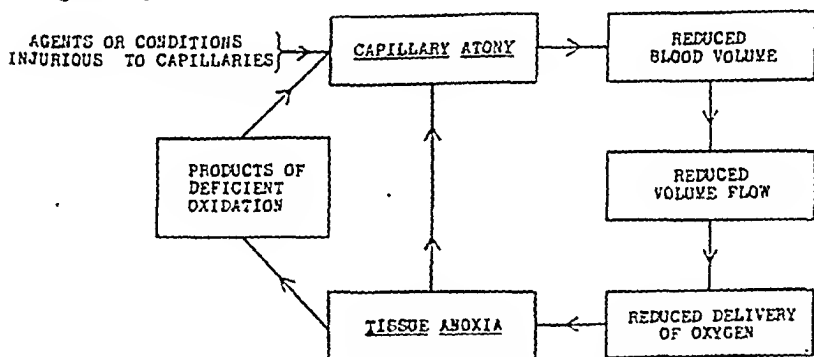


DIAGRAM 2—Reduction of both blood volume and of volume flow results from dilatation and abnormal permeability of capillaries. A reduced delivery of oxygen causes anoxia in the tissues. Lack of oxygen of itself causes dilatation and permeability of capillaries. This relationship gives the mechanism the character of a vicious circle.

In my opinion, the greatest obstacle to agreement has been that many regard *traumatic shock* as a separate entity, a disease condition *sui generis*. They have recognized no kinship between it and shock originating otherwise, nor have they sensed the importance of endothelial damage as an etiologic factor. Traumatic shock has this factor in common with shock from other causes. Hence many of the items of deranged physiology are identical, regardless of what conditions produced the endothelial effects.

A comprehension of these phenomena had to await an adequate understanding of endothelial reactions and capillary function. Studies on capillary physiology removed one major hindrance to a

comprehension of circulatory failure originating in the capillaries. Another major cause for confusion now awaits consideration.

Shock and the Effects of Hemorrhages. A decline in arterial blood pressure has long been regarded as the central feature in the syndrome of shock. Consequently every single factor which might account for the low blood pressure has been advocated as the primary cause. Myocardial weakness, vasomotor exhaustion, adrenal deficiency, acapnia, fat embolism and hemorrhage—each was proposed and, with the exception of hemorrhage, each was discarded because of incompatibility with known facts.

Space is lacking to review these theories and the facts which rendered each of them untenable. A new interpretation of shock resulted from evidence collected during the previous World War. As experiences with battle wounds accumulated, the conviction grew that absorption of products from injured tissues was a major factor in producing the circulatory deficiency. Surgeons testified that this deficiency was out of all proportion to the apparent severity of the wound and that it subsided in a remarkable fashion after débridement or amputation of the damaged limb.

"The explanation which had the strongest support, both from clinical observations and laboratory studies, was that of a toxic factor, arising from damaged and dying tissue and operating to cause an increased permeability of the capillary walls and a consequent reduction of blood volume by escape of plasma into the lymph spaces. Thus the concentration of the corpuseles is also readily explained."²⁰

Many factors contributed to the development of shock from wounds. Among these were hemorrhage, cold, delay in débridement or amputation, anesthesia, infection, improper splinting, rough transportation, loss of fluid by perspiration and by vomiting, and other items.

For several years this explanation of "traumatic toxemia" was widely accepted for it explained satisfactorily most of the observations on shock and it coincided with what was known of capillary reactions at that time.

Then the experiments and interpretations of several groups raised grave doubts concerning the accuracy of that explanation. Dogs were anesthetized deeply and their muscles were severely traumatized by bruising. Blood pressure readings were the sole criteria of shock. After death the amounts of blood and fluid, extravasated into the traumatized areas, were estimated and compared with the calculated blood volumes of the animals. In several series of such experiments, sufficient blood and fluid was found in the traumatized regions to account for the declining blood pressure and the death of the dogs without resort to the supposition that injurious substances had been absorbed from the damaged tissues.

In one group of experiments, the local extravasations of blood and

fluid ranged from 310 to 1057 gm. These represent serious hemorrhages indeed for dogs of average size. The traumatized limbs contained massive extravasations while the adjacent tissues were swollen and infiltrated with bloody fluid. The viscera as seen post-mortem were pale and ischemic. In view of these findings and of the *hemodilution* which preceded death, one must concur heartily in the authors' conclusions that hemorrhage was the predominant factor in these experiments. Any effects of absorption were so overshadowed by the effects of hemorrhage that they were unrecognizable.

The same method of experimentation produced similar results at the hands of other groups. These agreed in concluding that all the manifestations of traumatic shock are due to local loss of blood and fluid and that absorption of products from traumatized tissues is not a factor.

In 1932 attention was called²² to several important differences, both physiologic and morphologic, between shock and the effects of hemorrhage. That evidence was amplified and repeated several times in subsequent publications. Yet the belief prevails widely that all the manifestations of shock may result from simple hemorrhages alone. The evidence supporting this belief requires critical examination.

No one has published a detailed comparison of shock with the effects of hemorrhage, yet many significant features of these conditions have been contributed by different workers. They present several points of similarity, because any type of circulatory deficiency evokes compensatory reactions by the sympatho-adrenal system.

Similarities Between Shock and the Effects of Hemorrhage.

Activity of the sympatho-adrenal system causes:

Stimulation of myocardium; strong rapid pulse in early stages.

Peripheral vasoconstriction; reduced volume flow; peripheral ischemia and declining temperature; loss of tissue turgor.

Discharge of reservoir blood into systemic circulation; contraction of spleen.

Increased blood sugar.

Dilatation of pupils, often perspiration.

Low basal metabolism.

Decreased alkaline reserve.

Decreased serum protein.

Increased respiratory rate, thirst.

Declining arterial blood pressure (in late stages).

Death due to inadequate circulatory function.

The reactions enumerated are the same in either case, which fact explains several clinical resemblances between shock and hemorrhage. Because of these resemblances, it was assumed that the

two conditions are identical. But a more penetrating scrutiny reveals other totally different departures from physiologic constants. For purposes of comparison, these are arranged in tabular form.

<i>Items.</i>	<i>Shock.</i>	<i>Hemorrhage.</i>
Endothelium	Permeable to colloids	Impermeable to colloids
Tissue fluid	Increased	Decreased
Flow of lymph	Increased	Decreased
Fluid balance	Disturbed	Undisturbed
Pulmonary edema	Progressive	None
Absorption, gastro-intestinal	Impaired	Unimpaired
Absorption, from tissues	Impaired	Unimpaired
Vomiting	Persistent	No vomiting
Diarrhea	Frequent	Absent
Transfusion of blood	Often ineffective	Effective
Saline solutions, intravenous	Ineffective	Often effective
<i>Blood:</i>		
Hemoglobin, erythrocytes	Increased	Decreased
Specific gravity	Increased	Decreased
Non-protein nitrogen	Increased	Decreased or unchanged
Potassium	Increased	Terminal increase
Calcium	Increased	Decreased
Magnesium	Increased	Decreased
Chlorides	Decreased	Unchanged
Congulation time	Lengthened	Shortened
<i>Urine</i>	Concentrated, low volume, albumin, erythrocytes, casts, urobilinogen, acetone	No characteristic changes
<i>Necropsy findings:</i>		
Edema	Characteristic	None
Serous effusions	Present	Absent
Capillo-venous congestion	Characteristic	Absent
Petechiæ	Characteristic	Absent
Visceral ischemia	Absent	Present
Organ weight	Increased	Decreased
Gastro-intestinal tract	Dilated, atonic	Contracted
Parenchymal necroses	Present	Absent

It seems remarkable that such noteworthy differences should have escaped the attention of those who have written extensively on the effects of hemorrhages as related to shock. Let it be emphasized that hemorrhage or local loss of fluid is a highly important factor contributing to shock but the assumed identity of these conditions and of their *modus operandi*, is incongruous with a mass of physiologic evidence.

Failure to distinguish between shock and the effects of hemorrhages was the second major cause for conflicting interpretations.

Sources of Error in Mode of Experimentation. Attention is now invited to the third major cause for confusion, comprising sources of error inherent in the method of experimentation. On first entering this much disputed territory, my associates and I followed the paths travelled by our predecessors, including the mode of experimentation. The method in common use was to anesthetize an animal deeply with barbitol or otherwise and then to inflict some form of trauma, using records of the arterial pressure as an index of

circulatory effects and of the animal's condition. In one of our earliest experiments, a dog was given sodium phenobarbital intravenously, 0.3 gm. per kilogram, and an artery was cannulated for kymographic record. Although no trauma had as yet been done, the pressure began a progressive decline of 93 mm. Hg within 2 hours. We immediately abandoned barbital as an anesthetic and lost much of our confidence in conclusions based upon such experiments. Evidently our predecessors had had similar experiences for several authors reported that some of their dogs developed "spontaneous shock" under barbital anesthesia. Blalock³ stated: "In several animals there was a rapid decline in the blood pressure shortly after giving the barbital. These experiments were discarded. The level of the mean blood pressure was used as a criterion of the degree of shock." This statement implies that, if experimentation had begun before barbital caused the pressure to fall, the results of those experiments were considered dependable.

Gruber and Baskett¹³ reported that barbital and sodium phenobarbital, in doses comparable to those used in experimental work, caused a fall in blood pressure in 162 out of 164 tests. Seever and Tatum²⁶ confirmed the effects of these drugs upon the circulation. Medical military records show that frequently a wounded soldier, whose condition was not critical, developed profound shock immediately when anesthetized for operation. Dale⁷ and his associates produced fatal shock in etherized cats by injections of 1 or 2 mm. of histamine, but unanesthetized cats withstood 10 times that dosage. Complete anesthesia, while usually insufficient to produce circulatory failure of itself, comes dangerously near the threshold level in many instances. The barbiturates in the dosage used for anesthesia in animals approach the danger point closely.

It seems remarkable that investigators have overlooked the effects of deep narcosis upon the blood pressure. When variations in pressure are used as a criterion of shock, the importance of this factor of error is incalculable. It appears that the depressor effects observed in such experiments resulted from a combination of factors, any one of which may cause a decline in blood pressure. The experimental conditions may be analyzed as follows:

Let X	symbolize	the effects of	hemorrhage and loss of fluid;
" Y	"	"	" anesthesia;
" Z	"	"	" absorption from damaged tissues.

Then shock, as indicated by a decline in the blood pressure, is represented by the formula:

$$X + Y + Z = \text{Shock}$$

Evaluation of an equation containing two or more unknown quantities is as illogical in medical science as in mathematics. It is absurd even to assume that those quantities will have the same relative values in any two experiments, for their nature is essentially

that of indeterminate variables. Under such conditions of experimentation the recorded phenomena may be due either to the narcotic, or to absorption, or to the associated hemorrhage, or in part to each. Yet, ignoring the effects of absorption and of anesthesia, the conclusion was drawn that the entire circulatory disturbance resulted from hemorrhage and loss of fluid locally.

It may be stated with emphasis that this combination of indeterminate variables is responsible for much confusion and lack of agreement in interpretations. This statement does not imply criticism of any author or group; it merely directs attention to serious defects and sources for error inherent in methods commonly used for experiments on shock.

The Pathologic Anatomy of Shock. Last but not least of the causes for divergent interpretations was failure to apply to the problem the methods used by pathologists. The belief had been accepted, apparently without question, that shock is purely a physiologic disturbance unaccompanied by significant morphologic changes. It was not realized that in this, as in other conditions of disease, valid interpretations find corroboration in the accompanying morphologic alterations.

My colleagues and I made a series of experiments for the dual purpose of testing the effects of products absorbed from damaged tissues and of studying the circulatory changes seen in the viscera after death by shock.

The Effects of Absorption. A method was devised to determine what effects would follow the absorption of substances derived from bruised or damaged tissues. Fresh, finely ground, muscle pulp introduced into the peritoneal cavity of normal dogs caused progressive circulatory deficiency having all the characteristics of shock.²² These did not differ in any particular from the effects of extensive burns, histamine, peptone poisoning, or anaphylaxis. In such experiments, hemorrhage and narcosis were eliminated for no hemorrhage occurred and the brief ether anesthesia, given while opening the abdomen, had passed off hours before circulatory effects developed. Other tissues, as brain, liver or kidney, produced similar effects. Watery extracts of the tissues mentioned or of intestinal mucosa disturbed the circulation in a similar manner. By such methods it was possible to eliminate two complicating factors from the conditions of experimentation and to evaluate the effects of absorption alone. In each instance shock accompanied by hemoconcentration resulted from the absorption or the injection of the substance mentioned, uncomplicated by the effects of hemorrhage or of anesthesia.

Morphologic Evidence. The visceral appearances after death were indicative of endothelial relaxation in extensive visceral areas.^{21a, 23} Briefly summarized, these include capillo-venous congestion of the liver, kidneys, gastro-intestinal mucosæ, lungs, and of the serosæ.

Frequently there are petechial hemorrhages in these tissues, in the meninges and occasionally in the brain. When death is somewhat delayed, the soft tissues are edematous and there are effusions of fluid into the serous cavities. The visceral changes described had been noted many times^{21c} in both experimental and clinical shock but without comment on their possible significance. These changes appear directly related to endothelial damage as described earlier in this discussion. They indicate the effects of agents or conditions which have altered seriously the structure and function of the capillaries.

Exactly similar pathologic alterations were seen in the viscera after death from $HgCl_2$ poisoning, eclampsia, intestinal strangulation, acute pancreatitis, burns and after infections of unusual severity. They were seen also after shock produced experimentally by a wide variety of agents. These findings indicate that circulatory disturbances, originating in the capillaries, may result from various types of injury but that in each instance the clinical, physiologic and pathologic features are identical in kind.

Several writers have attributed shock resulting from trauma or burns, to loss of plasma locally, as edema and blister fluid, about the injured areas. Such loss of fluid often is important as a contributory factor, but *local* permeability and transudation of fluid do not explain the *visceral* congestion and edema which accompany shock from tissue injury. The occurrence of such changes in areas remote from the injury indicates systemic, not local, effects. If a colloidal dye, such as trypan blue, is injected into the blood during the development of shock, areas of thoracic and abdominal tissues become stained diffusely with the dye. This indicates endothelial permeability in extensive regions, not limited to those about the injury.

A significant item of evidence, bearing on the underlying vascular dynamics, is the occurrence of edema of the lungs and other soft tissues after shock from diverse causes. This suggested that perhaps pulmonary edema might be produced experimentally by inducing shock of sublethal degree or in degrees not immediately fatal. Accordingly, experiments were devised to test this possibility.²³ Shock with delayed death, resulting from repeated subcutaneous injections of histamine, from burns, from injections of bile, from intestinal obstruction and from other conditions, caused marked pulmonary edema accompanied by hemoconcentration. This result corroborated the belief that endothelial permeability in extensive areas is a major factor in the mechanism involved (see Fig. 1).

Lungs whose circulation is impaired, and whose spaces are filled with albuminous fluid, present ideal conditions for the development of infection. A common type of hemorrhagic edematous pneumonia²⁴ develops almost inevitably as a terminal event if neither death nor recovery from shock occurs soon.

Recent Theories. Two recent theories concerning the origin of shock are based upon the physiologic reactions by which systemic disturbances are compensated. These theories appear diametrically opposed, for one of them interprets shock as the *inadequacy* of the mechanism of compensation, while the other explains it as the result of *compensatory hyperactivity*.

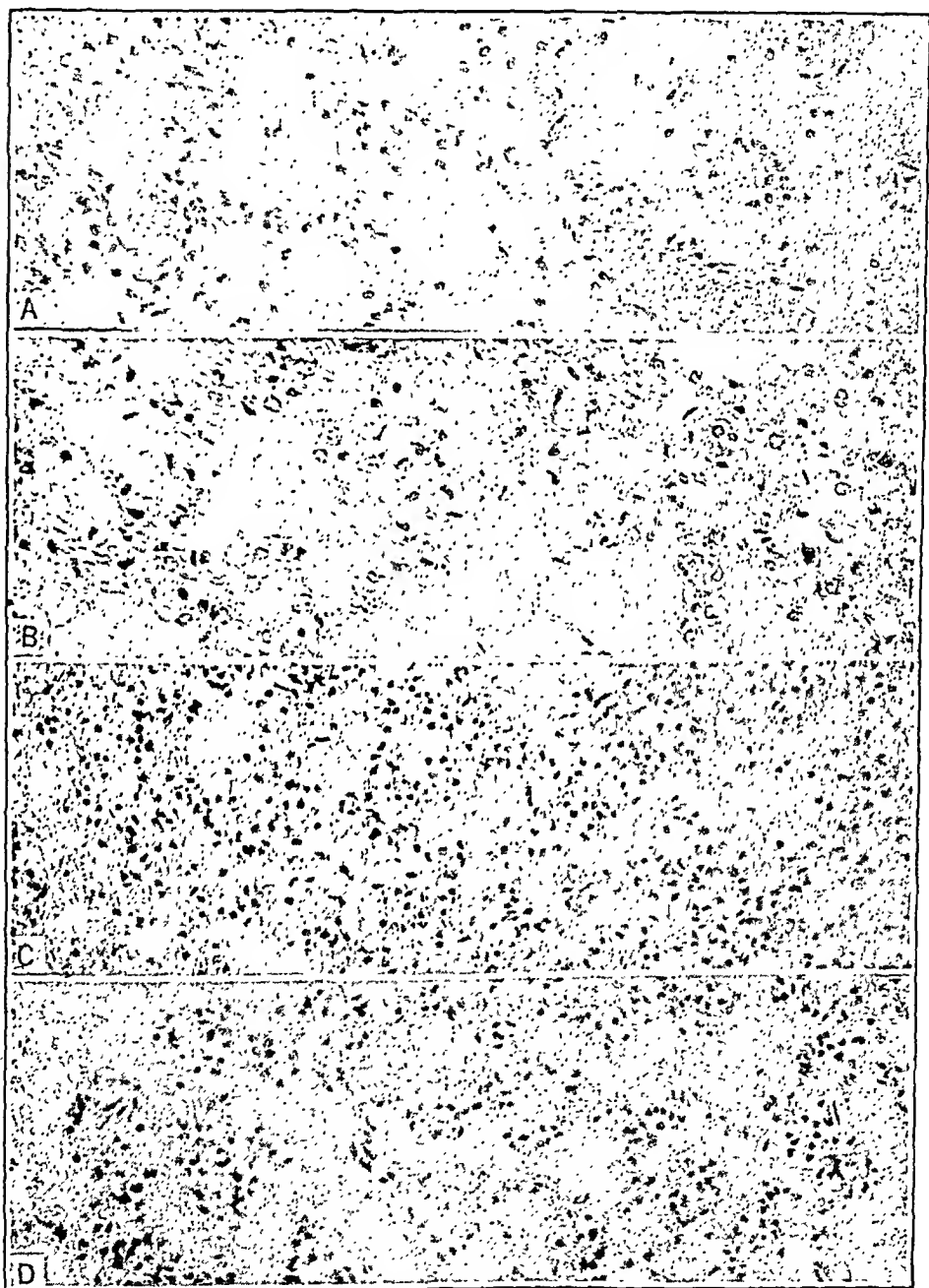


FIG. 1.—Experimental pulmonary edema. A, by subcutaneous injections of histamine; B, by scalding of the skin; C, by muscle pulp in the peritoneum; D, by intestinal strangulation.

The Alarm Reaction. Selye^{7a,b} has called attention to a syndrome which appears when severe injury is inflicted upon the animal organism. This syndrome is independent of the nature of the damaging agent and represents a response to damage as such. Exposure to cold, traumatic injuries, excessive muscular exercise, spinal shock, anaphylaxis, acute infections and intoxications with various drugs will evoke this syndrome, which is interpreted as an expression of general defense.

The term *alarm reaction* is applied to the sum total of the biologic phenomena elicited by the sudden effects of damaging agents. It represents a "call to arms" of all the resources which tend toward adaptation or defense. Shock itself is defined as a condition of suddenly developing intense systemic (general) damage and is described as occurring in two phases, *shock* and *counter-shock*.

The first phase is characterized by the usual physiologic features and clinical signs of shock. This phase is interpreted as one of relative adrenal insufficiency. Death may follow if the degree of adaptability is limited, *i. e.*, if the defensive resources are inadequate to counteract the damage.

If the first phase does not end fatally, it is followed by the second phase, that of counter-shock, consisting of a reversal of most of the items mentioned and a return toward normal physiologic conditions.

This conception omits essential parts of the problem from consideration. Others have studied the mechanism by which damaging agents disturb normal functions; Selye has focussed attention on the physiologic resources for counteracting the damage. The former say the animal dies from the systemic effects of the damage; the latter attributes death to inadequacy of the defensive reactions. Obviously, interest should not be limited to the dynamics of the damaging agents but should include also the counteractive mechanisms. However, shock interpreted as inadequacy of the physiologic defenses presents an uncompleted picture. One still would inquire by what mechanism is the circulation disturbed and why are the metabolism, fluid balance, renal function and chemical concentrations altered. These important items in the syndrome of shock can hardly be interpreted as adaptive or defensive in character.

Hyperactivity of the Sympatho-adrenal System. It is known that injections of epinephrin in large amounts will cause the complete syndrome of shock (Bainbridge,¹ Erlanger,⁸ Lamson¹⁸ and others). The resulting vasoconstriction eventually leads to an oxygen deficit in the tissues with ensuing capillary dilatation and permeability of endothelium, thereby initiating a progressive circulatory deficiency. Freeman^{10,11} believes that, in response to pain or emotions and to the injury itself, hyperactivity of the sympatho-adrenal system produces a similar effect. This is offered as an explanation for shock resulting from trauma, burns, hemorrhages and other causes.

A critical examination of the evidence reveals several points of

seeming incompatibility with known facts. Conditions accompanied by prolonged intolerable pain, such as renal or biliary colic, do not cause shock nor can it be produced experimentally by prolonged stimulation of nerve trunks. The sympatho-adrenal systems of men and animals are called into maximal activity during physical combat. Yet no instances of shock have been noted under these conditions, independent of serious wounds or hemorrhage.

Neither cutting the spinal cord nor severing all nerve paths from the traumatized area will prevent the development of shock. Animals previously subjected to bilateral sympathectomy (Freedlander and Lenhart⁹), also adrenalectomized animals (Swingle and associates^{29a,b}), develop shock from trauma or from other causes as readily as do normal animals. Hyperactivity of the sympatho-adrenal system would appear to be eliminated in such experiments.

The immediate treatment of an extensive burn, as with tannic acid, will prevent shock or lessen its degree. It is not probable that such treatment reduces the sympatho-adrenal response to the tissue damage nor to the pain and fright of the accident.

Finally, it has been shown that deep Roentgen irradiation of the abdomen causes the complete syndrome of shock in dogs, accompanied by hemoconcentration and by distinctive visceral changes as described. Roentgen irradiation is an agent which, like heat, causes tissue injury. It is followed by delayed necrosis of the glandular epithelium in the intestinal mucosa and the development of shock is delayed correspondingly. Warren and Whipple³¹ believed that absorption of products from the tissues damaged by Roentgen rays resulted in progressive deficiency of the circulation, and recent investigations³⁴ have supported that view. Irradiation is painless and whatever emotional responses it might cause would subside shortly. The dogs appeared entirely normal on the following day. No anesthesia was used, nor was there hemorrhage nor local loss of fluid. Such conditions provide no apparent cause for the development of sympatho-adrenal hyperactivity several days later.

The chief experimental evidence supporting this theory was derived from a comparison of the effects of hemorrhages and transfusions in two groups of dogs. For reasons not entirely clear, the normal dogs were subjected to far greater losses of blood than the sympathectomized ones. The authors concluded that the latter were more resistant to the effects of hemorrhage. Since shock and the effects of hemorrhage are not identical (*vide supra*), these experiments may not bear directly upon the problem. If the authors have tested the effects of trauma or of other shock-producing agents upon sympathectomized dogs, the results have not been published.

It appears that more definite evidence will be required before hyperactivity of the sympatho-adrenal system can be considered seriously as a major factor in the mechanism of shock.

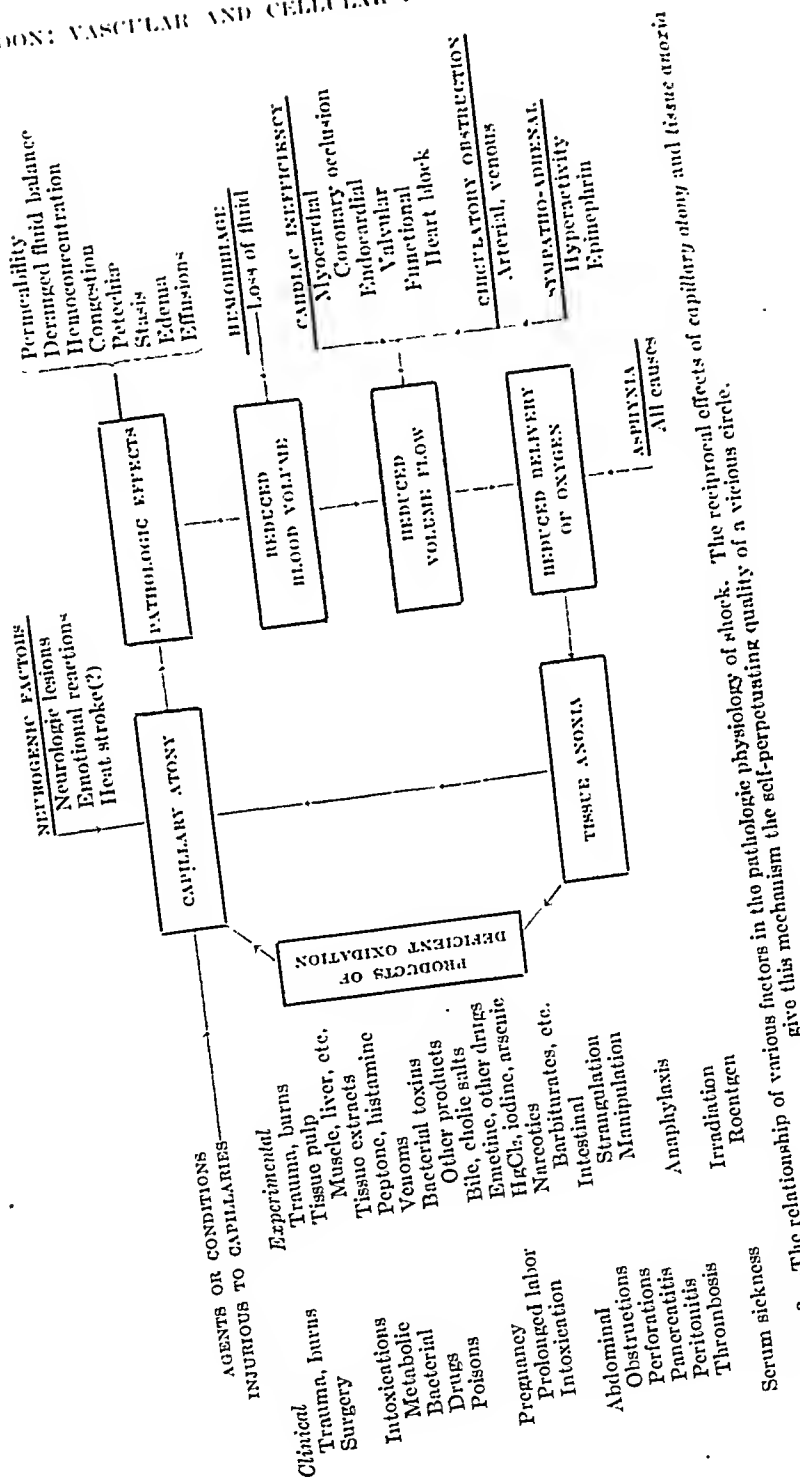


DIAGRAM 3.

Summary. An analysis of the sources for disagreement concerning the dynamics of shock indicates that four major causes have operated to confuse interpretations of its phenomena and of their interrelationships.

The first of these was deficient knowledge of capillary reactions and of circulatory disturbances originating in them. A comprehension of these has contributed immeasurably to an understanding of shock resulting from trauma, burns and other types of tissue damage. It clarifies also the disturbances of fluid balance and of chemical concentrations which are associated regularly with this condition.

Failure to distinguish between shock and hemorrhage has caused much confusion. Hemorrhage, when present, is a potent contributory factor, but the effects of uncomplicated hemorrhages present numerous features opposite in character from those which constitute the syndrome of shock.

Variations in blood pressure used as a criterion, and failure to consider the depressor effects of both anesthesia and losses of blood, have led to undependable conclusions concerning the effects of absorption. Varied forms of experimentation have shown that products derived from normal tissues, independent of narcosis and hemorrhage, will produce the syndrome of shock accompanied by its characteristic physiologic and morphologic features.

Hemoconcentration during life, and the presence of engorged capillaries, stasis, petechiæ and edema after death, indicate endothelial damage as a major factor. The occurrence of these conditions in extensive visceral areas remote from the injury indicates systemic, not local, endothelial damage. Shock, like other conditions of disease, is accompanied by a pattern of morphologic changes which are related etiologically to its mechanism of origin and which corroborate the interpretation of shock as due to endothelial damage.

The major causes for disagreement concerning shock have been discussed. In view of the character and magnitude of these, it is not strange that final clarification of the problem has been delayed. When these causes have been recognized and obviated, it becomes a simple matter to assemble the related facts into an intelligible picture. This diagram presents that picture as we see it.

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OBSERVATIONS ON THE ETIOLOGIC RELATIONSHIP OF ACHYLIA GASTRICA TO PERNICIOUS ANEMIA.

IX. DIFFERENCE IN SITE OF SECRETION OF INTRINSIC FACTOR IN THE HOG AND IN THE HUMAN STOMACH.*

BY HERBERT J. FOX, M.D.,

ASSISTANT IN MEDICINE, HARVARD MEDICAL SCHOOL; ASSISTANT RESIDENT PHYSICIAN,
THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL,

AND

WILLIAM B. CASTLE, M.D.,

PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL; ASSOCIATE DIRECTOR, THORNDIKE MEMORIAL LABORATORY; DIRECTOR, SECOND AND FOURTH MEDICAL SERVICES (HARVARD), BOSTON CITY HOSPITAL,
BOSTON, MASS.

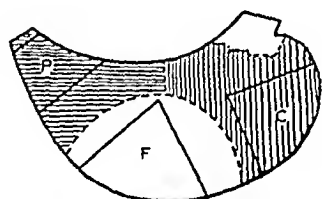
(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services [Harvard], Boston City Hospital, and the Department of Medicine, Harvard Medical School.)

In previous observations^{1,2} it has been demonstrated that the fasting normal human gastric juice contains a principle (intrinsic factor) which, when administered with beef muscle (extrinsic factor) to patients with Addisonian pernicious anemia, causes increased blood production and clinical improvement. Because neither human saliva nor pure duodenal secretion was effective upon admixture with beef muscle,⁴ it was tacitly assumed that the so-called intrinsic factor was secreted in man by that portion of the stomach which in pernicious anemia exhibits atrophy or disappearance of the normal glandular structure.^{5a,b,5,9b} Except by inference from the work

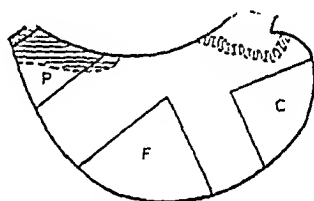
* The expenses of this investigation were defrayed in part by the J. K. Lilly Gift to the Harvard Medical School.

with hog stomach preparations carried out by Meulengracht,^{9a,c} Ungley¹⁸ and others, and from experimental gastrectomies in animals, no physiologic evidence on the localization of the source of intrinsic factor in the normal human stomach is available.

The technique utilized by Meulengracht was to test in patients with pernicious anemia the blood-forming activity of desiccated preparations of hog stomach after division into cardia, fundus and pylorus portions, respectively. Meulengracht^{9a,b,10} deduced from such observations and from studies of the comparative histology of the hog and human stomachs that the "pyloric gland organ" in both species is the principal site of secretion of intrinsic factor. This conclusion involves, however, two fundamental assumptions: 1, that the presence in desiccated hog stomach preparations of material possessing blood-forming activity in pernicious anemia defines the site of secretion of intrinsic factor; and 2, that such observations with the hog stomach are directly applicable to man. The purpose of the present investigation was to determine the validity of these two assumptions; especially because, as both Meulengracht^{9b} and Magnus and Ungley⁸ have recently pointed out, the degenerative process in the stomach in pernicious anemia does not significantly involve the "pyloric gland organ," inferred by Meulengracht to be the chief source of intrinsic factor in man.



(A) HOG STOMACH
FIG. 1A



(B) HUMAN STOMACH
FIG. 1B

FIG. 1A.—Distribution of pylorus, cardia and fundus type of glands in hog stomach (shaded areas P and C and clear area F) according to Meulengracht and Ohlsen.¹⁰ Solid lines indicate plan of incisions for pylorus, cardia and fundus preparations of hog stomachs according to Meulengracht and Schipdt¹¹ and as employed in the present observations for pylorus and fundus preparations of hog stomachs.

FIG. 1B.—Distribution of pylorus (horizontal shading), cardia (vertical shading) and fundus (clear area) type of glands in human stomachs according to Paschke and Orator.¹³ Plan of incisions (solid lines) employed for pylorus, cardia and fundus preparations of human stomachs was identical with that employed for hog stomachs.¹¹

General Methods. Various preparations of hog and human stomachs were secured in the following manner, except as indicated in the description of certain individual observations. The stomachs of freshly killed hogs were collected and divided into those portions defined by Meulengracht^{9b} as fundus and pylorus, as shown in Figure 1A. After removal of adherent fat and brief washing with cold water, the wet weight of each pylorus portion averaged about 60 gm. and that of each fundus portion about 100 gm. An appropriate number of specimens of each portion were then finely ground and spread on shallow pans for desiccation in a current of air at room temperature. In certain observations indicated below, the mucosa

was removed and ground with beef muscle. After from 24 to 48 hours the film of dried material was scraped from the pan and ground in a mill. It was then carefully defatted with ether, further pulverized and placed in a desiccator over soda lime for final drying. Thereafter the dry, powdered material was stored in glass-stoppered bottles out of the light, until required for use.

Human stomachs were removed at postmortem examination, usually within 12 hours and always within 24 hours after death. The subjects providing this material were all adults, of both sexes and of various ages, who had died suddenly of cardiac or cerebral lesions and in whom there was no clinical or postmortem evidence of infection of any type. Immediately after removal, the stomachs were freed of adherent fatty tissue and divided arbitrarily into the three portions defined by Meulengracht for the hog stomach, as shown in Figure 1A. The average wet weights of the three portions of the stomach were: pylorus 20 gm., fundus 23 gm., cardia 18 gm. Appropriate numbers of specimens of each portion were then briefly rinsed in cold running tap water and ground with an equal weight of beef muscle. Thereafter the material derived from each portion was desiccated, defatted and stored as described above. When finally ready for use, all the preparations were odorless, homogeneous, grayish-white powders weighing approximately one-fourth the wet weights of the original tissues.

The blood-forming activity of these preparations in pernicious anemia was determined by the effect of their daily administration to suitable patients, especially by the presence or absence of significant reticulocyte responses, the interpretation of which has previously been fully described.¹² Unless otherwise indicated, 10 gm. of each preparation was given 3 times daily for 10 days; and if the material under test produced no response, the ability of the patient to react was determined in an immediately subsequent period by the administration of an active experimental preparation or of 10 gm. of Ventriculin (N.N.R.) 3 times daily for 10 days. The methods of dietary control and of reticulocyte and red blood cell counting have been described in detail in previous publications.^{1,2,4}

The Blood-Forming Activity of Desiccated Preparations of Various Portions of the Hog Stomach as an Indicator of the Site of Secretion of Intrinsic Factor. The correctness of the assumption that the blood-forming activity of desiccated hog stomach is due to the presence of the so-called intrinsic factor is suggested by the following observations: 1, the active principle of hog stomach, like that of normal human gastric juice, is relatively thermolabile, each being destroyed by boiling for 5 minutes or by incubation at from pH 2.5 to 3.5 for 48 hours;^{1,4} 2, boiled hog stomach mucosa, itself ineffective, becomes capable of blood formation in pernicious anemia after admixture with normal human gastric juice.¹ Nevertheless, the fact that the combined work of Sharp,¹⁶ Meulengracht,^{9a,c,d} Thompson,¹⁷ Uotila,¹⁹ Ungley,¹⁸ Schemensky¹⁴ and others indicates that preparations of every portion of the alimentary tract of the hog, *with the exception of the fundus of the stomach*, are effective in causing increased blood production in pernicious anemia raises the question whether the experimental techniques employed by Meulengracht^{9a,c,d} and Ungley¹⁸ could be, in any way, responsible for their failure to obtain activity with fundus preparations. Thus, it is conceivable that the apparent ineffectiveness of the fundus might have been due to

local destruction of intrinsic factor, to failure of the fasting animal to secrete sufficient intrinsic factor, to the presence of intrinsic factor in a zymogen form or to the necessity, after secretion, of its activation of or by substances contributed by the pylorus region of the stomach. These theoretical possibilities were accordingly investigated.

The first undertaking was to determine whether the method employed for desiccation and defatting was capable of preserving the well-established anti-anemic activity of a hog stomach pylorus preparation. Positive evidence for this was obtained by the administration of 30 gm. of a desiccated, defatted mixture of equal wet weights of hog stomach pylorus mucosa and of beef muscle daily for 10 days. As shown in Table 1, Case 81, there was a significant effect on blood production during this period.

Meulengracht's and Ungley's observation that the feeding of desiccated hog fundus preparations does not cause increased blood production in pernicious anemia was confirmed by the negative results of the daily administration of 30 gm. of desiccated hog fundus during the first period of observation of Case 82, who responded satisfactorily to the administration of Ventricleulin (N.N.R.) during a third period of observation. In the second period the possibility was investigated that the presence of hydrochloric acid and pepsin in the fundus during the process of desiccation might have been responsible, in Meulengracht's experiments, for the destruction of intrinsic factor and consequently for the absence of anti-anemic activity. Indeed, Meulengracht and Schjødt¹¹ have shown that the fundus of the hog stomach is the chief source of pepsin and is the only portion of the stomach in which stimulation of secretion by histamine injection causes an acid reaction to Congo red paper. Moreover, it has been demonstrated⁴ that the incubation at 37.5° C. of hog stomach mucosa at from pH 2.5 to 3.5 for 48 hours completely destroys its blood-forming activity. And, finally, it has been shown that intrinsic factor is partially destroyed by incubation of normal human gastric juice at pH 1.5 for 2 hours,¹ but is not affected by such treatment at pH 10.⁶ Accordingly, in order to afford to any intrinsic factor present the maximum protection against acid or against enzymes active at an acid reaction, the fundus portion of the hog stomach was removed immediately and was finely ground with an equal weight of water. To this was added about 4 cc. of normal sodium hydroxide per 100 gm. of fundus, which was found to be a sufficient amount to produce a reaction of pH 7.2. Nevertheless, as shown in Table 1, this neutralized fundus preparation, like the unneutralized preparation, produced no detectable effect on blood formation in Case 82, although in a third period of observation* the patient responded to the daily administration of 30 gm.

* Not shown in Table 1 because of lack of space.

TABLE 1.—EFFECT OF DAILY ORAL ADMINISTRATION IN PERNICIOUS ANEMIA OF VARIOUS DESICCATED AND DEFAECATED HOG STOMACH PREPARATIONS.
(Dosage = 30 gm. daily, unless otherwise indicated.)

Days of treatment.	CASE 81.		CASE 82.		CASE 83.		CASE 84.		CASE 85.		CASE 86.		CASE 89.	
	R.B.C., mill.	Retics., %	R.B.C., mill.	Retics., %	R.B.C., mill.	Retics., %	R.B.C., mill.	Retics., %	R.B.C., mill.	Retics., %	R.B.C., mill.	Retics., %	R.B.C., mill.	Retics., %
	First Periods.													
	Fundus.				Neutralized fundus (obtained after food and histamine injection).				Acidified fundus and beef muscle.				Fundus after stand- ing for 24 hours.	
0	1.39	2.4	1.40	1.6	1.63	0.4	1.12	2.2	1.12	2.2	1.90	2.0	1.90	2.0
2	1.32	2.0	1.27	0.8	1.58	1.0	0.98	2.0	0.98	2.0	2.30	2.0	1.91	1.2
4	1.06	4.6	1.27	0.6	1.59	0.6	1.12	1.2	1.12	1.2	2.48	3.0	1.79	0.4
6	1.07	7.8	1.27	2.2	1.63	1.0	1.02	0.2	1.02	0.2	2.41	3.2	2.05	0.4
8	1.24	14.8	1.24	3.1	1.54	1.0	0.97	0.6	0.97	0.6	2.25	10.4	2.17	1.0
10	1.34	20.6	1.20	2.2	1.48	0.8	0.91	1.0	0.91	1.0	2.47	8.8	1.74	—
12	1.43	17.4	—	—	—	—	—	—	—	—	2.66	4.0	—	—
14	1.12	13.2	—	—	—	—	—	—	—	—	2.93	2.4	—	—
	Second Periods.													
	Neutralized fundus.				Ventriculin (N.N.R.).				Ventriculin (N.N.R.).				Pylorus mucosa 10 gm., fundus 50 gm., beef muscle 50 gm. (28 gm. dry weight).	
2	1.18	2.8	1.65	0.6	0.99	0.4	1.06	1.4	0.99	0.4	2.63	5.0	2.14	0.2
4	1.13	0.2	1.57	1.0	1.20	4.2	1.26	14.4	1.06	1.4	2.84	4.0	2.13	2.2
6	1.02	2.0	1.59	1.8	1.26	14.4	1.46	11.4	1.20	4.2	2.64	2.2	2.32	1.8
8	0.95	2.2	1.41	6.6	1.46	11.4	—	—	1.26	14.4	2.62	1.8	2.25	7.8
10	1.37	2.8*	1.53	9.8	1.46	11.4	—	—	1.46	11.4	2.80	1.6	2.68	3.6
12	—	—	—	—	—	—	—	—	—	—	—	—	—	—
14	—	—	—	—	—	—	—	—	—	—	—	—	—	—

* A subsequent 21% reticulocyte response to Ventriculin (N.N.R.) on the 10th day of a third period is not shown.

of Ventriculin (N.N.R.). For example, on the 10th day the reticulocytes reached a peak value of 21%.

Because Meulengracht did not state whether the fundus preparations utilized in his work were obtained from fasting hogs or from hogs which had previously been fed, the possibility that his negative results with fundus were due to an inadequate stimulus to secretion of intrinsic factor was investigated in the following manner. Approximately $1\frac{1}{2}$ hours before slaughtering, hogs were fed a mixture of milk and cornmeal, and about 1 hour later each was given an intramuscular injection of 3 mg. of histamine hydrochloride. As soon as the fundus portion of the stomach had been dissected, it was finely ground in an equal weight of cold water and the reaction adjusted to pH 7.2 with about 4 cc. of normal sodium hydroxide per 100 gm. of fundus. Thereafter, the material was desiccated and defatted as usual. As shown in Table 1, Case 83, during the first period of observation the daily administration of 30 gm. of this desiccated preparation was quite ineffective, whereas in the second period the daily administration of 30 gm. of Ventriculin (N.N.R.) caused a moderate reticulocyte response.

The next possibility investigated was that intrinsic factor might become active only after secretion into an acid medium such as exists in gastric juice; that is, just as for the activation of pepsin from its zymogen form, hydrochloric acid might be essential for the activation of intrinsic factor. It is true that this appeared to be unlikely because of previous demonstrations^{3,7} of intrinsic factor in gastric juice containing no free hydrochloric acid. Nevertheless, to fresh preparations of hog stomach fundus was added an equal weight of water and sufficient strong hydrochloric acid to effect a reaction of about pH 2 after thorough grinding of the material. The acidified fundus pulp was allowed to stand in the icebox for 1 hour. It was then ground with an equal weight of beef muscle, and the reaction of the mixture brought to approximately pH 6.5 with strong sodium hydroxide. Thereafter the material was desiccated, defatted and fed to Case 84 in a dosage of 30 gm. daily during the first period of observation. As shown in Table 1, it produced no significant effect on blood formation, although in the second period of observation the daily administration of 30 gm. of Ventriculin (N.N.R.) was distinctly effective.

In his most recent publication on this subject, Meulengracht^{9b} considers the possibility that the fundus portion of the normal stomach might supply a hormonal "pacemaker" for the production of intrinsic factor by the pylorus region. Another hypothesis consistent with his observations is that intrinsic factor, though secreted by the fundus, might become active only upon contact with the pylorus mucosa, or with some secretion of that portion of the stomach. Accordingly, this possibility was examined. As shown in Table 1, in the first period of observation of Case 85 the daily

administration of 28 gm. of a desiccated preparation derived from a mixture of 10 gm. of fresh pylorus mucosa and 100 gm. of beef muscle had a powerful effect on blood production. In Case 86 the possibility of potentiation of fundus by admixture with pylorus mucosa was tested. In the first period of observation, the effectiveness of the daily administration of 28 gm. of desiccated material derived from 10 gm. of pylorus mucosa and 100 gm. of beef muscle was confirmed. In the second period, 28 gm. of a desiccated preparation derived from 10 gm. of pylorus mucosa, 60 gm. of whole fundus and 50 gm. of beef muscle, administered daily, was not shown to possess greater hematopoietic activity.

Thus, attempts at securing evidence of the presence of intrinsic factor in hog stomach fundus preparations by neutralization, by stimulation of secretion, by preliminary acidification before neutralization and by admixture with pylorus tissue all failed. These observations appear completely to confirm the experiments of Meulengracht, Ungley and others purporting to show that whereas desiccated preparations of the fundus of the hog stomach have no effect on blood production in pernicious anemia, similar preparations of the pylorus region are highly active. Their assumption that the distribution of such blood-forming activity is an indication of the site of secretion of intrinsic factor in the hog stomach is thus entirely supported by the present observations.

Difference in Site of Secretion of Intrinsic Factor in the Hog and in the Human Stomach. Meulengracht^{9b} and Magnus and Ungley⁸ have pointed out the apparent conflict between the existing physiologic and histologic evidence on the site of secretion of intrinsic factor in the human stomach. Thus, their feeding experiments^{9a, c, 18} with desiccated hog stomach preparations indicate that the fundus of the hog stomach does not contain intrinsic factor, whereas their careful histologic studies^{8, 9b} in pernicious anemia confirm the fact, observed by others,^{5a, b} that in this condition the fundus of the human stomach is the region of degeneration. Meulengracht's experiments demonstrating the hematopoietic activity of both desiccated hog stomach pylorus and duodenum led him to infer that the "pyloric gland organ," regarded as including the region of Brunner's glands of the duodenum and the histologically similar pyloric glands, is likewise in man a source of intrinsic factor. This conclusion is, however, in conflict with the normal histologic appearance of the pylorus and duodenum in pernicious anemia^{8, 9b} and with physiologic evidence from observations on man. Thus, it has been demonstrated⁴ that although normal human duodenal contents which include gastric juice contain intrinsic factor, when gastric secretion is excluded from the duodenum intrinsic factor is no longer present in the secretion collected therefrom. It therefore appeared to be possible that these discrepancies might depend upon a species

difference between man and the hog as to the site of secretion of intrinsic factor.

Accordingly, the blood-forming activity in pernicious anemia of desiccated preparations of the human stomach was determined after arbitrary division into three portions, "pylorus," "fundus" and "cardia," respectively, according to Meulengracht's plan for the hog stomach, which is shown in Figure 1A. The fact that the nomenclature applied to these divisions of the human stomach does not, as in the hog stomach, correspond with areas of different gland structure was clearly recognized and will be discussed below. To each freshly excised and washed portion of the stomach was added an equal weight of beef muscle. The details of the subsequent desiccation, defatting and storage of the preparations have been described above. As shown in Table 2, Case 87, the daily administration of 30 gm. of the pylorus preparation during the first period of 10 days caused a slight reticulocyte response. There was no clinical improvement. No significant increase in red blood cells occurred until during the second period when, as a result of the daily administration of 30 gm. of Ventriculin (N.N.R.) for 10 days, there was a significantly greater reticulocyte response and marked clinical improvement. In the first periods of observation of Cases 88 and 89, when 30 gm. of a fundus preparation and of a cardia preparation, respectively, was administered daily for 10 days, striking reticulocyte responses and clinical improvement occurred. During the second periods, the daily feeding of 30 gm. of Ventriculin (N.N.R.) to each case resulted in no detectable second rise of reticulocytes.

TABLE 2.—EFFECT OF DAILY ORAL ADMINISTRATION IN PERNICIOUS ANEMIA OF DESICCATED AND DEFATTED HUMAN STOMACH PREPARATIONS.

(Dosage = 30 gm. daily.)

Days of treatment.	CASE 87.		CASE 88.		CASE 89.	
	R.B.C., mills.	Retics., %.	R.B.C., mills.	Retics., %.	R.B.C., mills.	Retics., %.
<i>First Periods: Human Stomach Preparations.</i>						
	Pylorus preparation.		Fundus preparation.		Cardia preparation.	
0	1.62	1.8	1.80	0.8	1.44	1.8
2	1.69	0.8	1.59	0.9	1.42	2.0
4	1.44	0.4	1.68	5.0	1.37	3.1
6	1.46	1.0	1.69	19.2	1.57	11.6
8	1.47	2.0	1.86	25.3	1.64	27.8
10	1.54	6.4	2.14	16.2	1.99	18.6
<i>Second Periods: Hog Stomach Preparation (Ventriculin N.N.R.).</i>						
	Ventriculin.		Ventriculin.		Ventriculin.	
2	1.55	4.9	2.57	2.8	2.18	16.6
4	1.50	3.4	2.67	3.9	2.12	6.8
6	1.49	8.9	2.79	1.0	2.34	4.4
8	1.60	8.1	2.58	0.8	2.11	4.6
10	1.51	10.8	2.74	1.2	2.04	4.3
12	1.85	18.8	2.60	1.2	2.42	3.4
14	2.39	16.5				

A possible criticism of these observations is that whereas the hog stomachs were obtained immediately after the death of the animals, the human stomachs were secured usually within 12 hours but sometimes between 12 and 24 hours after death. Accordingly, although these postmortem conditions did not destroy the potency of the human material, the question arises whether the distribution of activity might have been modified by prolonged contact post-mortem of one portion of the stomach with secretion from another. As a control on such postmortem effects in the human material, preparations were made from hog stomachs previously subjected to the following procedure. Immediately after removal from the hogs, the pyloric and esophageal orifices of the stomachs were occluded with a tightly tied ligature. The unopened stomachs were allowed to stand at room temperature for 6 hours and were then placed in the icebox for an additional 18 hours. Thereafter the stomachs were opened, the food and gastric secretions were removed, and specimens of the pylorus and fundus were excised, washed, desiccated and defatted in the usual manner. In the first period of observation of Case 90, shown in Table 1, the daily administration of 30 gm. of the fundus preparation was found to be without effect, but in the second period the pylorus preparation caused increased blood production. Thus, despite contact with gastric contents for 24 hours after death, the fundus preparation of the hog stomach remained hematopoietically ineffective. By analogy, therefore, it seems proper to assume that the distribution of the activity of the human stomachs was not modified by postmortem effects.

Discussion. According to these observations, the blood-forming activity of desiccated preparations of the human stomach after arbitrary division into areas resembling the pylorus, fundus and cardia portions of the hog stomach, as defined by Meulengracht, had a distinctly different distribution from that obtaining in similar areas of the hog stomach. Thus, the so-called fundus and cardia preparations of the human stomach were highly effective, whereas the pylorus was, at best, weakly active compared with Ventriculin (N.N.R.) in the dosage specified. The observations reported in the first portion of this paper lend weight to the validity of Meulengracht's assumption that the distribution of the anti-anemic potency is an indication of the site of secretion of intrinsic factor in the stomach of the hog. Application of the same assumption to the present results with desiccated human stomach preparations leads to the conclusion that in man the areas here arbitrarily designated as "fundus" and "cardia," but not the "pylorus" region of the stomach, are the important sites of the formation or secretion of intrinsic factor. If reference is made to the histologic studies of the human stomach by Paschkis and Orator,¹³ the type of glandular structure presumably present in each of these areas may be determined. According to these authors, the pyloric glands in the

human stomach are found in an area extending along the lesser curvature to the angulus, or about 6 cm. from the pylorus, but along the greater curvature run only a very short distance from the pylorus. The cardiac glands are confined to an area a few millimeters in width adjacent to the border of the esophageal mucosa. The fundic glands occupy the rest of the stomach wall. Reference to the approximate outlines of these areas shown in Figure 1*B* indicates that the so-called pylorus preparation of the human stomach may have contained a considerable proportion of fundic glands, whereas the so-called fundus and cardia preparations contained fundic glands only. There is, thus, no question but that in these human stomachs the fundus type of gland was associated with anti-anemic activity. Indeed, the weakly positive effect observed with the so-called pylorus preparation might also be ascribed to the presence of fundic glands.

According to this evidence, then, the site of secretion of intrinsic factor, as defined by the hematopoietic activity of desiccated human stomach preparations, is found to correspond to the site of the degenerative process^{5*a*,*b*,*8*,*9b*} in the stomach in Addisonian pernicious anemia, a disease in which it is clear that intrinsic factor is deficient. The present observations, suggesting the relative insignificance of the "pyloric gland organ" as a source of intrinsic factor in man, are in agreement with the previous observation⁴ that pure duodenal secretion in man does not contain detectable amounts of intrinsic factor. Thus, with the exception of the recent report of Schenken, Stasney and Hall,¹⁵ all the observations which have been made on man point to the fundic gland area of the human stomach as the important source of intrinsic factor. The evidence becomes contradictory only when conclusions which undoubtedly obtain for the hog are directly translated to man.

Conclusions. 1. By means of observations under controlled conditions on patients with Addisonian pernicious anemia, the previous experiments of Meulengracht, Ungley and others concerning the effectiveness of desiccated preparations of the pylorus and the ineffectiveness of similar preparations of the fundus of the hog stomach were confirmed.

2. It was not possible to develop an active fundus preparation of hog stomach by measures designed: *a*, to prevent the local destruction of intrinsic factor; *b*, to increase its secretion; *c*, to activate a zymogen form; or *d*, to potentiate intrinsic factor by contact with substances in the pylorus region of the stomach.

3. These facts contribute support to Meulengracht's assumption that the anti-anemic potency of the pylorus region of the hog stomach indicates it as a site of secretion of intrinsic factor in that animal.

4. Application of this assumption, however, to the present observations with desiccated preparations of normal human stomach

suggests the conclusion that in man those areas containing the fundus type of gland, and not the "pyloric gland organ," are the important sites of secretion of intrinsic factor.

5. The present observations suggest that the source of intrinsic factor in the normal human stomach coincides with the site of the degenerative process seen in histologic preparations of the stomach in pernicious anemia.

6. Because the cardia of the human stomach is apparently an active site of secretion of intrinsic factor, gastric resections in man which preserve this portion of the stomach should, theoretically, provide a source of intrinsic factor for the patient.

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RELATIONSHIP BETWEEN THE SPLEEN AND THE MORPHOLOGIC PICTURE OF BLOOD REGENERATION.

By W. O. CRUZ, M.D.,

FROM INSTITUTO OSWALDO CRUZ, RIO DE JANEIRO, BRAZIL, VISITING FELLOW OF THE ROCKEFELLER FOUNDATION, SCHOOL OF MEDICINE AND DENTISTRY, PATHOLOGY DEPARTMENT, ROCHESTER, N. Y.

AND

F. S. ROBSCHUIT-ROBBINS, PH.D.,

ASSOCIATE IN PATHOLOGY, ROCHESTER, N. Y.

(From the Department of Pathology, The University of Rochester School of Medicine and Dentistry.)

PRESENT concepts of blood physiology attribute but little of essential importance to the function of the spleen. As far as the main splenic functions—lymphocyte production and destruction of old erythrocytes—are concerned, other organs of the body economy can replace the spleen adequately. The rôle of the spleen as a

reservoir is not of primary importance and only in some occasional occurrence can it have vital significance. Hormonal and anti-infectious properties of the spleen have been emphasized by some authors, but conclusive proof of their rôle has not yet been obtained.

It is very well known that any blood regeneration is characterized by a peculiar morphologic picture showing the launching of young red blood cells (reticulocytes) into the circulation. The main morphologic feature is the presence of a reticulum within the vitally stained new cells; when stained by Giemsa or Wright stain, these cells are polychromatophilic. These two staining methods reveal also the erythrocytes with nuclear structures as the normoblast and the erythrocyte with nuclear particles.

Very few papers concern themselves with experimental work that includes the complete morphology of blood regeneration. Only the reticulocytes have been carefully observed in human anemias and in experimental animals. In the earlier studies of the blood much attention was paid to the normoblasts and erythrocytes with nuclear bodies because they were the only morphologic signs of blood regeneration, but careful experimental studies have not been made. Drinker, Drinker and Kreutzmann² pointed out that a true normoblastic crisis in the peripheral blood of dogs occurs after hemorrhage just before the rapid increase in the erythrocyte count and usually towards the end of the first week following the hemorrhage. These authors observed only once a crisis of 8000 normoblasts per c.mm., 12 days after the last bleeding. Crises of 5600 (5 days after bleeding), 4000 (4 days after) and 3000 (9 days after) are reported together with other minor crises. Muller^{4a,b} observed normoblastic crises in rabbits after intravenous injections of India ink or gum shellac. With India ink the highest normoblast count found was 77,000 per c.mm., and counts above 20,000 per c.mm. were very often observed; with gum shellac the highest count was 80,000 per c.mm. and counts above 20,000 per c.mm. were easily verified. More recently Hamre and Miller³ produced anemia by deficient iron intakes in two different groups of rats—non-splenectomized and splenectomized. They then observed during blood regeneration following iron and copper administration, a normoblastic crisis in both groups, much higher in the splenectomized group. The greatest crisis occurred 2 days after the metal administration gave a count of 5000 normoblasts per c.mm. in the non-splenectomized group. The splenectomized group after the same 2 days indicated a rise to 33,000 normoblasts per c.mm. with a secondary rise of 10,000 per c.mm. on the sixth day.

The present paper deals with studies concerning the morphology of the blood during regeneration following anemia produced by hemorrhage or by acetylphenylhydrazine injections, in normal and splenectomized dogs.

Methods. Detailed observations were made in 6 non-splenectomized and 3 splenectomized dogs. The splenectomized dogs were observed at different time intervals following the splenectomy (Dog 40-115 was studied 2 months after the operation; Dog 39-194, 11 months after, and Dog 24-70, 2½ years after). Further observations were made also in 13 dogs belonging to the anemia colony. Different levels of anemia were produced by hemorrhage with the usual jugular puncture method or by subcutaneous injections of acetylphenylhydrazine, dissolved in hot saline solution (10 to 20 cc.) just prior to injection. Daily observations of the blood picture were made in 11 periods during blood regeneration. Red blood cell counts were made in the usual manner with Thoma micro-pipette and Neubauer counting chamber. Hemoglobin was determined by the oxyhemoglobin method in the Klett-Summerson photoelectric colorimeter. Reticulocytes were counted by direct microscopic observation of a drop of blood mixed with a drop of 1% solution of cresyl blue in saline solution. The normoblasts (orthochromatic erythroblasts of Ferrata) were counted in relation to number of erythrocytes in smears stained with Giemsa stain; the young erythroblasts (basophilic erythroblasts of Ferrata) were counted in the same manner. For comparative purposes a case of thalassemia (Cooley's anemia) was studied, since it is well known that this type of human anemia is characterized by large numbers of normoblasts in peripheral blood.

TABLE 1.—ACETYLPHENYLHYDRAZINE ANEMIA.

Days of observation.	Red blood cells (mil. per c.mm.).					Hemoglobin (gm. per 100 cc.).				
	Splenectomized dogs.		Non-splenectomized dogs.			Splenectomized dogs.		Non-splenectomized dogs.		
	39-194	40-115	40-213	39-137	39-299	39-194	40-115	40-213	39-137	39-299
1	*5.4	*5.6	*5.8	15.5	*7.3	12.0	12.7	12.9	13.5	9.9
2	*4.8	14.9	*6.5	8.2	..	9.6	11.5	8.4
3	*4.0	*5.1	*4.6	14.0	*6.0	7.5	10.7	9.5	8.5	6.7
4	*3.6	3.0	..	5.8	6.1	..
5	*2.8	*4.0	*3.0	2.0	3.1	..	7.9	5.6	4.4	3.9
6	..	3.6	*2.4	1.6	1.6	3.7	6.4	4.5	3.5	3.3
7	2.2	..	2.0	1.5	2.1	3.1	..	3.3	3.7	4.2
8	1.7	1.6	1.6	1.7	2.3	3.4	3.0	2.9	4.2	4.9
9	1.8	1.6	1.4	2.1	2.8	3.5	3.2	2.3	5.3	5.6
10	1.7	1.3	1.5	2.8	3.4	3.8	2.9	2.7	7.3	7.4
11	1.7	1.4	1.7	3.9	3.1	3.3
12	1.7	1.7	2.0	3.3	3.5	4.1	7.9	..
13	..	1.8	2.7	3.7	..	5.6	..	5.8	9.4	..
14	2.4	7.3
15	3.1	7.3
16	3.7	7.3	..	8.3
17	3.0	2.4	4.3	5.7	9.5
18

Dog 39-194—first day of observation is 11 months after splenectomy. Dog 40-115—2 months after splenectomy.

* Acetylphenylhydrazine, 300 mg. † Acetylphenylhydrazine, 200 mg. ‡ Acetylphenylhydrazine, 100 mg.

Observations and Discussion. Tables 1 and 1a present the results found in the acetylphenylhydrazine anemia. Table 1 shows that the lowest anemia levels are about the same in both groups of dogs, around 1,500,000 erythrocytes per c.mm., and 3 gm. hemoglobin in 100 cc. of blood. This is a very low level and all dogs became acutely sick for 2 or 3 days. The recovery from the anemia is always complete and very fast in both groups of dogs, showing that the spleen does not have any direct and indispensable function relating to the regeneration of this type of anemia. This same fact was observed by Robscheit-Robbins and Whipple⁶ during the

recovery of experimental hemorrhage anemia in dogs. Table 1a shows that the reticulocytosis is about the same in both cases, the highest number was 79% in the splenectomized group (Dog 39-194), and 77% in the normal one (Dog 40-213). A sharp difference between the two groups is found in the number of normoblasts and basophilic erythroblasts. In the non-splenectomized dogs the highest normoblast count was 6000 per c.mm. (Dog 40-213), whereas in the splenectomized group was observed 25,000 per c.mm. (Dog. 39-194) and 22,000 (Dog 40-115), with 6 other figures above 10,000 per c.mm. The highest basophilic erythroblast count in the normal group was 700 per c.mm. (Dog 39-299), 16% when calculated in proportion to the normoblasts. The splenectomized group, on the other hand, demonstrated the highest count of 4300 per c.mm. which is 43% as related to the normoblasts. The peak of the normoblast crisis appears when the red blood cell begins to rise, and the basophilic erythroblast crisis follows 2 or 3 days thereafter when the normoblasts are going down. Those smears with 43% of basophilic erythroblasts are very interesting in this respect, and resemble the morphologic picture of severe human pernicious anemia during megaloblastic crisis.

TABLE 1A.—IMMATURE CELLS IN ACETYLPHENYLHYDRAZINE ANEMIA.

Days of observation.	Reticulocytes (%).					Normoblasts (thous. per c.mm.).					Ratio basophilic erythroblasts to normoblasts (%).			
	Splenectomized dogs.		Non-splenectomized dogs.			Splenectomized dogs.		Non-splenectomized dogs.			Splenectomized dogs.		Non-splenectomized dogs.	
	39-194	40-115	40-213	39-137	39-299	39-194	40-115	40-213	39-137	39-299	39-194	40-115	40-213	39-137
1	2	0.2	5	0.5	0.5	0	0	0	0	0	0	0	0	0
2	3	1	0.5	0	0	0	0	0
3	3	0.5	4	2	..	0	0	0	0	..	0	0	0	0
4	5	3	2	0	0	1.8	0	0
5	24	2	18	13	0	0.1	0	1.4	0.3	0	..	3
6	32	3	17	25	10	4.2	0.2	1.0	0.2	1.2	4	3
7	33	..	26	22	21	11.0	..	0.9	0.5	1.2	4	7
8	69	21	50	23	27	19.0	6.3	0.8	1.1	3.2	4	13
9	79	26	77	26	32	11.0	9.1	2.1	..	1.6	2	..	6	..
10	70	26	67	26	23	0.7	2.5	4.0	1.3	1.0	2	..	10	9
11	37	14	52	..	12	0.5	6.2	5.3	..	0.5	1	4	3	..
12	35	17	32	19	..	0.6	18.0	6.0	0	0	7	14	4	0
13	19	..	30	9	10	14.0	22.0	6.0	0	0	5	12	12	0
14	24	25.0	4.3	0	0	0	27	14	10	0
15	..	15	19	..	4	0.6	0.5	1.7	0	0	43	..	11	0
16	8	4	..	10.0	..	1.1	0	0	43	..	6	0
17	9	9	2	3.5	0.6	37
18	2.4	25

Dog 39-194—first day of observation is 11 months after splenectomy; Dog 40-115—2 months after splenectomy.

Table 2 shows the results obtained with anemia by bleeding in 2 splenectomized dogs. The absolute number of normoblasts and basophilic erythroblasts here are much lower than in the acetylphenylhydrazine experiments, probably because the red cell level was considerably higher. Notwithstanding this the results obtained differ markedly from those obtained in normal dogs, in which it is well known that the normoblasts are very scarce during the recovery of this type of anemia.⁶

CRUZ, ROBSCHIEFF-ROBBINS:

TABLE 2. ANEMIA BY HEMORRHAGE.

[illegible]

TABLE 3.—Dog 24-70, SPLENECTOMIZED ANIMAL.

Date.	Red blood cells (mil. per c.mm.).	Hemoglobin (gm. per 100 cc.).	Normoblasts (thous. per c.mm.).	Ratio basophilic erythroblasts to normoblasts (%).	Observations.
1927-12-19	1.3	3.0			
1928- 1- 3	3.4	6.7			
1- 9	3.6	9.3	57.0	33	
1-16	3.0	9.3			
1-23	4.1	10.8	31.0	23	
2-27	2.3	6.5			
3- 5	3.6	9.9	44.0	13	
4-21	..	7.2			
5- 1	3.4	9.0			
5- 8	..	10.9	77.0	8	7th day after hemor- rhage (395 cc.)
5-31	..	6.2			
6- 4	1.8	..	20.0	15	6th day after hemor- rhage (190 cc.)
6-11	..	8.7			
6-28	3.2	6.2	11.0	18	6th day after hemor- rhage (165 cc.)
7- 2	3.4	6.5			
7- 9	..	8.5			
12- 3	4.5	5.5			
12-10	..	6.5	19.0	19	6th day after iron administration
12-17	3.4	9.7			

Table 3 indicates the most intense normoblastic crises observed. Blood smears and counts obtained once each week for a year's period of splenectomized Dog 24-70, were available for study. Examining this material we found 7 instances of marked normoblastic crises, all of which were related to regenerative periods as shown in the table. Perhaps these high normoblastic crises are

related to the fact that this dog was observed $2\frac{1}{2}$ years following splenectomy, whereas the other 2 splenectomized dogs were studied for only 2 and 11 months respectively following the operation. In 4 instances we observed as Drinker and associates pointed out, the peak of normoblastic crisis occurred one week following the hemorrhage.

For comparison concerning the high human normoblastosis, we studied a case of anemia (thalassemia, Cooley's anemia) which showed the following results: C. J., female, aged 8: Red blood cells, 2,200,000 per c.mm.; hemoglobin, 4.6 gm. per 100 cc. blood; normoblasts, 70,000 per c.mm.

TABLE 4.—NORMOBLASTOSIS DURING LOW AND ACTIVE REGENERATION PERIODS.

During low regenerative period			During active regenerative period.		
Dog No.	Average Hb. output per week (gm.).	Normoblasts (thous. per c.mm.).	Dog No.	Average Hb. output per week (gm.).	Normoblasts (thous. per c.mm.).
37-21	2	0	34-146	36	0.3
37-89	2	0	36-14	60	0
37-87	2	0	40-26	37	0.3
35-4	2	0.6	39-77	40	0
37-22	2	0	39-2	45	0
39-1	2	0	35-6	40	0
			32-4	37	0.9

Previous experience indicated that the normoblasts were not numerous during the regeneration period following anemia by hemorrhage in dogs, or in human anemias due to iron deficiency.¹ In order to obtain quantitative data of this subject, as well as for purposes of checking previous results, sinears of 13 dogs were carefully studied. The results are given in Table 4 representing findings obtained in 6 dogs during a low regenerative period (2 gm. of hemoglobin as a weekly output) and 5 dogs during periods of active regeneration (between 36 and 60 gm. of hemoglobin weekly).

It may be of interest to point out that the normoblasts are of minor importance in the morphologic picture of the blood in human anemias in which there are no marked spleen changes. The iron-deficient anemias (anemia of childhood, anemia of pregnancy, nutritional hypochromic anemia, hookworm anemia, recovery from acute hemorrhage) serve as examples. In contrast, the largest normoblastic crises found in human pathology are associated, at least in the majority of cases, with blood diseases in which the spleen is involved and the blood shows signs of regeneration such as malaria with splenomegalia, hemolytic icterus, sickle-cell anemia, and particularly in the Mediterranean anemia (thalassemia).

Summary and Conclusions. Detailed morphologic blood cell examinations were made in 3 splenectomized and 19 non-splenectomized dogs.

In the splenectomized dogs made anemic by bleeding or by acetylphenylhydrazine injections, the number of normoblasts in the peripheral blood during the first phase of the regenerative period

is four times greater than in the non-splenectomized animal. In some instances the number may be even higher, attaining 70,000 normoblasts per c.mm. Furthermore the number of primitive erythroblasts (basophilic erythroblasts of Ferrata) is much higher in the splenectomized animal, in some cases reaching about 40% of the nucleated red cells in the circulation.

These findings suggest a relationship between a function of the spleen and the maturation of the erythroblast in the bone marrow or a factor acting upon the launching mechanism of new red cells into the general circulation.

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THE HEART IN SICKLE CELL ANEMIA.

BY HARRY F. KLINEFELTER, M.D.,

ASSISTANT RESIDENT PHYSICIAN IN MEDICINE; INSTRUCTOR IN MEDICINE,
BALTIMORE, MD.

(From the Medical Clinic and Cardiographic Laboratory of the Johns Hopkins Hospital.)

SINCE 1910 when Herrick¹⁴ first described sickle cell anemia, many reports have appeared concerning the clinical, pathologic and hematologic aspects of this interesting disease. It has been said that these patients frequently suffer organic valvular disease of the heart.^{1a,6} The purpose of this communication is to analyze the clinical and pathologic material of this hospital in order to determine the incidence and extent of organic heart disease among patients with sickle cell anemia.

Many of the symptoms that are present during exacerbations of this disease are similar to those of acute rheumatic fever; and many of the cardiac signs observed during the quiescent stage closely resemble those of chronic valvular heart disease, particularly mitral stenosis.

In his original paper, Herrick¹⁴ described symptoms of exertional dyspnea, palpitation and recurring bouts of polyarthritis. His patient had an enlarged heart, with a loud systolic murmur over the whole precordium, and an accentuated second pulmonic sound.

In 1923, Huck¹⁵ described in detail the hematologic changes of sickle cell anemia and gave a full clinical description of 2 cases. In addition to the findings first noted by Herrick, 1 of Huck's patients had a protodiastolic gallop and both had slight edema of the ankles, slight enlargement of the liver, a rapid, labile pulse and low blood pressure.

During the next few years, other papers^{9,13,16,26} appeared, describing cases with cardiac enlargement, systolic murmurs, and accentuated second pulmonic sounds. Sydenstricker²⁶ was the first to report enlargement of the heart confirmed by Roentgen ray. He believed the polyarthritis, edema of the ankles and cardiac signs to be manifestations of the long-standing anemia. Hein, McCalla and Thorne,¹³ however, regarded the dyspnea as due to the anemia but considered the possibility that the cardiac signs, fever, leukocytosis and joint symptoms represented atypical rheumatic infection. They noted, however, that the response to salicylates was not so prompt as in rheumatic fever.

In 1932, Anderson and Ware^{1a,b} reviewed the literature and stated that cardiac enlargement was present in 76% and heart murmurs in 87% of the cases in which specific mention was made of their presence or absence. These authors came to the conclusion that the murmurs were probably functional but that organic heart disease was also present in many cases. Hamman¹¹ was the first to report an autopsied case of sickle cell anemia in which a definite diagnosis of rheumatic heart disease had been made. This was the first reported case in which diastolic murmurs were heard. Autopsy showed only a diffusely enlarged heart with normal valves and pericardium.

Although electrocardiograms had been taken on several patients,^{11,29} no definite abnormality was observed until 1933, when King and Janeway¹⁷ described a case with prolongation of the *P-R* interval. This finding in a young patient with cardiac abnormalities and recurring attacks of polyarthritis, fever, and leukocytosis made the possibility of rheumatic fever quite likely. This case (J. N.) is reviewed again in this report.

Postmortem findings were reported by many authors^{8,9,11,13,15,25,26,29} and the only abnormality found in the heart has been hypertrophy and dilatation. Steinberg²⁵ observed that the hypertrophy usually involved the left ventricle more than the right. Marked right ventricular hypertrophy was found by Yater and Hansmann²⁹ in 2 patients who died in right-sided heart failure. In these 2 cases, there were either small thrombi in the pulmonary arteries or tortuous, thickened pulmonary vessels which the authors felt explained the right-sided failure.

There is only one reported instance in which any endocardial abnormality was found. In Steinberg's case²⁵ on which no clinical data are given, there was "chronic verrucose endocarditis of the mitral and aortic valves with mononuclear infiltration and patchy necrosis of the myocardium." He thought these changes to be of atypical rheumatic origin. No other myocardial and no pericardial lesions have been noted.

Case Material. Twelve patients, 8 males and 4 females, from 8 to 27 years, with average age of 19, were selected from the clinics

of this hospital for this study. All have severe sickle cell anemia with hematocrit values ranging from 20% to 30%, and the average duration of the anemia is 11 years. Most of the studies of cardiac function were carried out after the patients had been in bed for several days in the hospital.

Of the 11 fatal cases, all followed in this hospital, autopsies were performed on 10 at this hospital and on 1 at the Baltimore City Hospital. In this group of fatalities there were 6 males and 5 females from 2 to 28 years, with an average age of 11, and the average duration of the anemia was 8 years.

All the patients in both groups were negroes.

Clinical Data. No effort will be made to record all the findings in the clinical study of the 12 patients now alive. Only the data relative to the cardiovascular system will be reviewed and analyzed in an effort to compare the heart in sickle cell anemia with that in other anemias and in rheumatic valvular disease.

One case is reported here in some detail in order to illustrate the difficulties that may be encountered in differentiating sickle cell anemia from rheumatic fever and rheumatic heart disease.

Case Report. CASE 1.—J. N. (Unit No. 122176, Patient 7, Table 1) was a 21-year-old unmarried negress who had been followed in this hospital for 12 years. At the age of 9, she was first admitted to the Harriet Lane Home because of an upper respiratory tract infection of 3 weeks' duration, with generalized aching, headaches, epistaxes, exertional dyspnea, and pain in the right chest suggesting pleurisy. She had suffered occasionally from anorexia and post-prandial vomiting for several years.

Examination showed a fairly well-developed child with pallor and slight general glandular enlargement. Temp. 100°. The tonsils were large and pale. There were a few fine moist râles at the lung bases. Pulse was rapid, regular, quick and full. A capillary pulse was present. Blood pressure 100/50. The heart was enlarged to right and left, with a readily visible precordial impulse. The point of maximum impulse was outside the nipple line in the fourth interspace. No thrills were felt. The heart sounds were normal except for an accentuated P_2 . A systolic murmur was present at the base and apex, and at the apex a low-pitched diastolic murmur was also present. The liver was enlarged but there was no abdominal tenderness, and there was no edema or orthopnea.

It was the impression of all who saw the patient that she had acute rheumatic fever and active rheumatic heart disease. There was a severe sickle cell anemia with leukocytosis. Roentgenogram showed cardiac enlargement and the electrocardiogram showed a heart rate of 107 with a $P-R$ interval of 0.18 to 0.20 second. She was treated with salicylates which had no apparent effect. Low grade fever, leukocytosis, and the anemia persisted, and she had frequent epistaxes but no joint pains. She remained on the ward 5 months during which time the cardiac murmurs persisted and frequent electrocardiograms continued to show a prolonged $P-R$ interval.

For the next 3 years, this patient was followed carefully in the Harriet Lane Clinic. At the age of 10, she had one attack of pain and swelling of the right ankle which lasted only 2 days. All the signs noted above persisted and a third heart sound appeared at the apex. The $A-V$ conduction time was always prolonged, varying from 0.20 to 0.25 second and the cardiac enlargement increased slightly.

TABLE 1.—SUMMARY OF SOME IMPORTANT CARDIOVASCULAR FINDINGS IN SICKLE CELL ANEMIA.

Case No.	Age.	Sex.	Hemato- crit, vol. c.c.	Exer- tional dysp- nea.	Murmurs.		Third heart sound.	Cardio- thoracic ratio, %.	Joint symp- toms.	P-R interval, sec.	B.P., mm. Hg.	Ven. pres- sure, mm. sa- line.	Circulation time.	
					Sys- tolic.	Dias- tolic.							NaCN, sec.	Paral- dehyde, sec.
1. J.H.	8	M	20	No	+	0	+	53.0	No	.16	105/50	80	14.0	..
2. E.C.	9	M	23	Yes	+++	+	+	53.8	Yes	.15-.24	100/50	65	9.0	5.0
3. L.N.	14	F	20	No	+++	+	+	55.1	No	.16	120/65	95	10.2	6.0
4. G.E.	19	F	20	Yes	++	0	+	52.7	Yes	.16	116/60	70	17.0	No
5. J.N.	20	M	30	No	+	0	+	51.8	Yes	.16-.24	120/70	125	19.0	end point No
6. E.A.	20	M	20	Yes	+++	+	+	51.0	Yes	.16-.21	130/50	70	10.0*	6.0
7. J.N.	21	F	27	Yes	+++	+	+	58.0	Yes	.18-.24	110/55	65	20.0	10.0
8. E.E.	22	M	20	Yes	++	+	0	48.7	Yes	.16	110/60	55	12.3	6.5
9. S.L.	22	M	30	No	+++	+	+	53.0	Yes	.16	100/60	60	12.0*	5.0
10. J.M.	26	F	20	Yes	++	+	0	59.3	Yes	.18-.23	115/50	95	15.6	7.0
11. L.H.	26	M	20	Yes	+++	+	+	54.0	No	.21-.25	118/64	100	14.0	8.0
12. D.J.	27	M	23	No	+	+	+	51.2	Yes	.18	120/60	40	17.0	8.0

* C.T.T. (2 cc.) used instead of sodium cyanide.

She continued to have frequent epistaxes and exertional dyspnea increased. She had episodes of polyarthralgia but was not disabled until the age of 15 when she suffered an acute exacerbation with fever, headache, epistaxis, and pain in the left knee. She was admitted to the Medical Service for study, although the arthralgia and fever had already subsided.

Examination showed a well-developed, adolescent negress with pallor and jaundice. The temperature was normal. The pulse was increased in rate, quick, and full, and there was a capillary pulse. Blood pressure 100/45. The heart was enlarged, with accentuated P_2 , loud systolic murmur at apex and base, and a third heart sound at the apex. Several observers heard a low-pitched rumble after the third sound. She had a marked anemia and leukocytosis. The P - R interval was slightly prolonged, 0.19 to 0.22 second. Roentgen ray showed cardiac enlargement without prominence of the pulmonary conus. Arm-to-tongue circulation time was 15 seconds with Decholin. Her course was marked by recurrent epistaxes and slow, slight improvement in the anemia.

At the age of 17, she was readmitted with severe pain in the left leg, ankle, and left side of abdomen. The onset was acute 3 days before admission and closely followed a mild upper respiratory infection. The patient voluntarily stated that the pain seemed to be in the bones rather than in the joints.

Examination showed no objective change in the joints but the left leg was extremely tender over the tibia. Cardiac findings were essentially as before. The anemia and leukocytosis persisted and the sedimentation rate was repeatedly normal, in spite of the severe anemia.* The A - V conduction time varied between 0.19 and 0.22 second. Roentgen rays showed no abnormality of the left tibia, but the cardiac enlargement persisted.

Salicylates were given a thorough trial and did not affect the pain; the left ankle actually became swollen during the course of treatment.

One year later, the patient had an acute attack of polyarthritis with some swelling of the shoulders, elbows, wrists, knees, and ankles. This

* This phenomenon has been shown by Bunting⁵ to be due to the presence of sickled cells.

cleared up in a few days but was followed by severe nausea and vomiting which required admission to the hospital. Temp. 101°. Blood pressure 105/60. The joints showed nothing abnormal. The cardiovascular system revealed the same abnormalities as on previous admissions, and the liver was enlarged. The anemia, leukocytosis, normal sedimentation rate, and prolonged *P-R* interval were still present. During the 6 weeks that she was on the ward, the patient had repeated attacks of abdominal pain, with and without fever, and contracted Type III pneumococcus pneumonia, during which the sedimentation rate increased.

During the 3 years since this last medical admission, she has had only occasional epistaxes and mild arthralgias in damp weather. Exertional dyspnea has not increased. Her main complaint has been repeated attacks of abdominal pain, usually in the right lower quadrant with nausea and vomiting.

Five months ago, at the age of 21, a normal appendix was removed during one of these attacks. The postoperative course was uneventful. Examination 4 days after operation revealed a well-nourished, intelligent negress with pallor and icterus. The heart was enlarged to right and left, with an overactive precordium. The pulse was quick and full. Blood pressure 110/55. The point of maximum impulse was in the fourth interspace 8 cm. to the left of the midline and the heart shifted with change of position. The sounds were loud, with accentuation of *P₂*. A loud systolic murmur was present at apex and base. A loud third heart sound was present at the apex and a stethocardiogram showed a short presystolic sound which could not definitely be distinguished on auscultation. The liver was felt 4 to 5 cm. below the costal margin. There was no edema, orthopnea or dyspnea.

The severe anemia was still present. The *P-R* interval was 0.20 second and the teleroentgenogram is shown in Figure 4. Venous pressure, circulation times, and vital capacity were within normal limits. Fluoroscopy showed diffuse cardiac enlargement with no displacement of the barium-filled esophagus.

The patient was discharged a week later and has not returned.

In summary, this 21-year-old negress has had severe sickle cell anemia for at least 12 years. She has cardiac enlargement with signs suggesting rheumatic mitral disease and acute episodes with arthritis, fever, abdominal pain, and leukocytosis suggesting rheumatic fever. *A-V* conduction time has been prolonged on numerous occasions. In spite of the long duration of her illness, she has never had myocardial insufficiency of any noticeable degree, and the left auricle is not disproportionately enlarged.

Symptoms. Nine of the 12 patients complain of recurring attacks of pain in the joints of the extremities, frequently with swelling, and occasionally with increased heat and redness. The involvement of the joints is occasionally migratory. The pain, however, is often not localized to the joints but also involves the long bones of the extremity. Several patients have had an inflammatory reaction in the joint with swelling, redness, increased heat, and pain on motion. Aspiration of one such joint yielded no fluid.

The bone and joint pains usually occur during a "crisis," which is frequently preceded by a respiratory tract infection. There is associated fever, icterus, and leukocytosis. The pain does not respond to salicylates. It seems probable that the symptoms in the extremities are due to a subperiosteal reaction, and occasionally changes in the periosteum can be found on Roentgen ray examina-

tion. None of the patients have had subcutaneous nodules or skin lesions other than leg ulcers.

None has so far exhibited frank evidence of congestive heart failure. This seems to occur only during the terminal stages. Seven of the 12 patients have exertional dyspnea, with or without palpitation, and 5 of these 7 are subject to the recurrent leg ulcers that are commonly associated with this disease. Two other patients with no exertional dyspnea also have leg ulcers. The ulcers are usually unilateral and it is interesting to note that there is usually a history of unilateral dependent edema of that extremity preceding the appearance of the ulcer.

No patient has dyspnea at rest, nocturnal dyspnea, orthopnea, precordial pain, or chronic cough.

Physical Findings. *General.* These patients are somewhat underdeveloped and undernourished, and a few are markedly retarded in their physical and mental development. One patient has many congenital bone abnormalities, including spina bifida, marked scoliosis, and tower skull. This latter abnormality is also present in several other patients. There is always pallor and a peculiar greenish-yellow hue to the scleræ. General glandular enlargement is very common. The liver is moderately enlarged to percussion but is difficult to palpate, does not pulsate and is not tender. The spleen is not now enlarged in any of these patients, although splenic enlargement was definite in 2 when they first came under observation 7 and 12 years ago. There is occasionally slight dependent edema of the ankles.

Fundus Oculi. Seven of the 12 patients have moderate to marked dilatation and tortuosity of the retinal veins, as shown in Figure 1. This has previously been reported by Harden.¹² This finding could not be correlated with the other cardiovascular abnormalities, the leg ulcers, or the duration of the anemia.

Cardiovascular. The pulse is normal in rate, quick but not collapsing, and of normal volume. There is frequently a sinus arrhythmia. Pulsations are prominent in the neck and often in the extremities. A capillary pulse is frequently visible, and pistol-shot sounds are often audible over the arteries. Duroziez's sign is rarely elicited. There is no venous distention, and the peripheral vessels are not sclerotic. The systolic blood pressure is normal, while the diastolic pressure tends to be low.

The precordium is overactive and this is often accentuated by the thin chest wall. There is a readily visible, diffuse, wavy impulse in the fourth, fifth and sometimes sixth interspaces to the left of the sternum. In cases with marked prominence of the pulmonary conus, there is a visible impulse and occasionally a bulge in the second and third interspaces to the left of the sternum. The point of maximum impulse is not well localized but is forceful and rolling, and there is a precordial lift. A diastolic tap is usually present in

the pulmonary area. A systolic thrill may be present over the precordium and vessels of the neck, but no diastolic thrill has been noted.

The heart is enlarged both to right and left and frequently there is increased dullness in the region of the pulmonary conus.

At the apex the first sound is louder than normal but not snapping. There is always a systolic murmur of variable intensity which is maximal early in systole and may be loud enough to obscure the first sound. The second sound is accentuated and in nearly every case there is a third heart sound early in diastole. No definite diastolic murmur is heard until presystole when there is often a questionable presystolic murmur blending with the first sound.



Right Eye.

Left Eye.

FIG. 1.—Photograph of ocular fundi (D. J., Patient 12, Table 1) showing typical tortuosity and dilatation of the retinal veins.

At the base, there is a systolic murmur at the pulmonary area which may be louder than the systolic murmur at the apex. P_2 is markedly accentuated and occasionally split. No diastolic murmurs are definitely heard at the base. There may be a systolic aortic murmur transmitted to the vessels of the neck.

The heart shifts freely with change of position, and there are no signs of mediastino-pericarditis.

Roentgen Studies. The teleroentgenogram constantly shows cardiac enlargement. The heart is enlarged to both right and left and the enlargement increases as the patients develop. In 8 cases, the pulmonary conus is definitely more prominent than normal (Fig. 2). In 2 of these 8 cases, the pulmonary conus is extremely prominent (Fig. 3). In this patient (Fig. 3), a kymogram shows pulsations of branches of the pulmonary arteries. In 2 cases, the cardiac outline is globular (Fig. 4). The cardiothoracic ratio is increased in every case, with an average of 53.5%.

All the patients had a fluoroscopic examination with barium in

the esophagus and in no instance was there any displacement by a disproportionately enlarged auricle. The pulmonary conus appeared more prominent with the fluoroscope than in Roentgen ray films and the pulsations of the conus were more marked than the other heart borders. The cardiac enlargement seemed to involve all the chambers equally.

Electrocardiogram. At least one electrocardiogram was taken on every patient and frequent records were obtained on many. The striking abnormality was prolongation of the *P-R* interval in 50% of the patients (Table 1). This will be discussed more fully in another section.

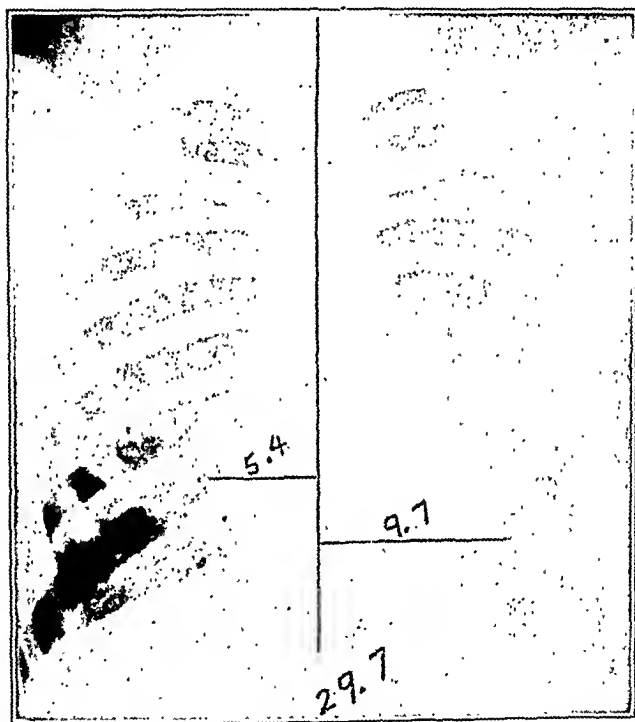


FIG. 2.—Teleroentgenogram (D. J., Patient 12, Table 1) showing cardiac enlargement with moderate prominence of pulmonary conus.

Sinus arrhythmia was frequently present and extrasystoles, usually of ventricular origin, were of common occurrence. Indeed, 1 patient had trigeminy and quadrigeminy which was thought clinically to be auricular fibrillation.

The *T* waves were sometimes altered, being unusually high in some tracings and lower than normal in others. The character of the *T* waves varied from time to time in the same patient. There was no significant axis deviation. Frank evidence of myocardial damage was lacking.

Stethocardiograms. Simultaneous electro- and stethocardiograms were taken on 9 of the 12 patients, principally to determine whether

there was a presystolic element in the sound at the apex. The portable Cambridge apparatus was employed, using Lead II for the electrocardiogram and the bell microphone to record the heart sounds. All the records were taken with the patients recumbent or semirecumbent.

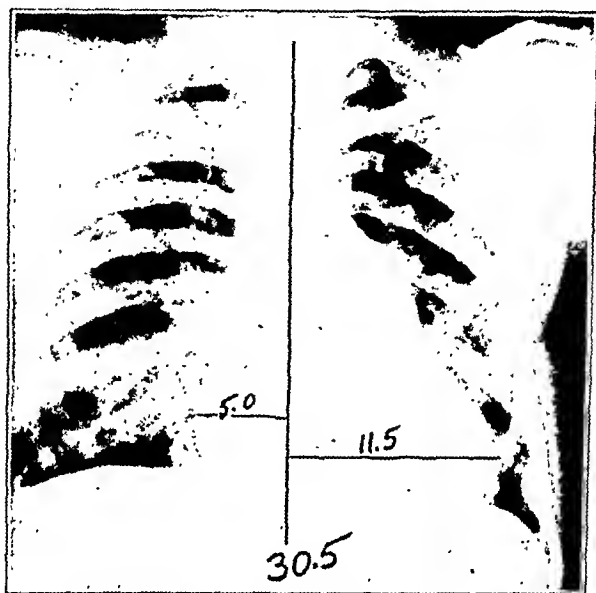


FIG. 3.—Teleroentgenogram (L. H., Patient 6, Table 1) showing cardiac enlargement with extreme prominence of pulmonary conus.

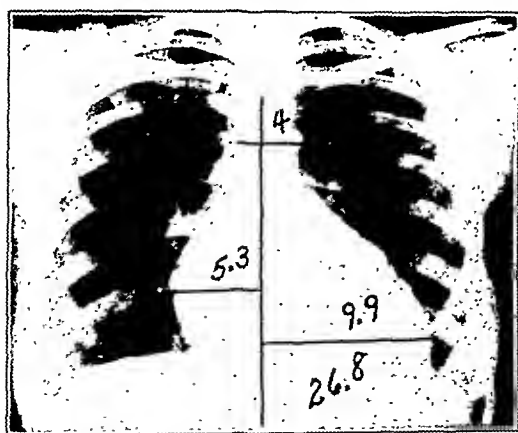


FIG. 4.—Teleroentgenogram (J. N., Patient 7, Table 1) showing diffuse cardiac enlargement with a globular configuration.

A typical record is shown in Figure 5. It is readily seen that there is a short, low-pitched presystolic sound which starts 0.10 sec-

ond before the first sound and 0.06 second before the *R* wave of the electrocardiogram. This occurred to a variable degree in all of the 9 patients and is indicated in Table 1 by a "+" under diastolic murmurs. This presystolic element was in general longer when the third heart sound was louder, but its intensity was not related to the length of the *P-R* interval.

The first sound is loud, but of normal pitch and is followed by a medium-pitched systolic murmur of moderate intensity which extends throughout most of systole. The second sound is slightly accentuated and followed by a short low-pitched sound of moderate intensity which is in the location of the normal third heart sound. Diastole is otherwise clear.

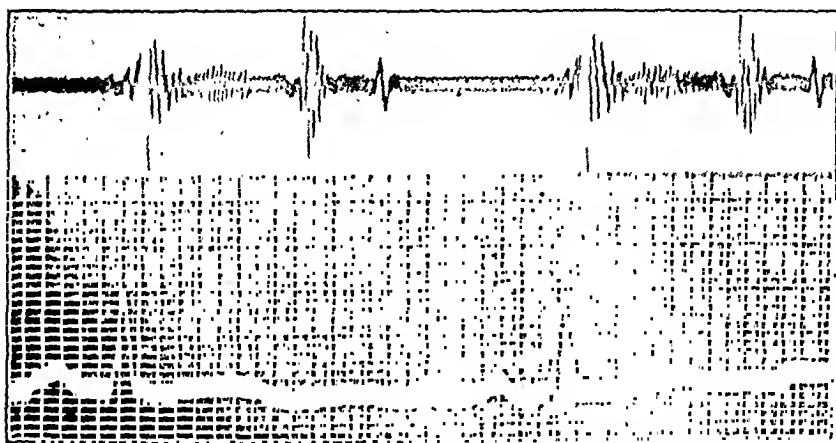


FIG. 5.—Stethocardiogram (D. J., Patient 12, Table 1) showing short presystolic murmur, systolic murmur, and third heart sound.

Tests of Cardiac Function. *Venous Pressure.* Determined by the direct method, this varied between 55 and 125 mm. saline (Table 1). Patient 6 (E. A.) was found to have a venous pressure of 200 mm. the first day of his fourth hospital admission 3 years ago.

He had a mild streptococcal pharyngitis without fever, an enlarged liver, slightly distended cervical veins, and minimal edema of the ankles but no orthopnea or basal râles. The urine contained albumin (3+). On bed rest, the venous pressure fell to normal and the patient lost 2 pounds in 4 days. His venous pressure has not been found elevated since that time.

Circulation Times. In 10 patients, the arm-to-carotid sinus time was determined by the sodium cyanide method.²¹ In the other 2, the arm-to-throat time was determined by the use of C.T.T. substance.²⁴ The arm-to-lung time was determined by the use of paraldehyde intravenously⁶ (Table 1). In no instance were the circulation times definitely abnormal. It is interesting to note that they were not accelerated as is frequently the case in anemia.

Vital Capacity. No significant reduction from the estimated normal was found in those patients who were intelligent enough to coöperate.

P-R Interval. As noted above, a prolonged *A-I* conduction time was found in 6 of the 12 patients. The degree of prolongation varied considerably in each of the 6 patients, and in any given patient the *P-R* interval tended to increase as the heart rate decreased. The records of these 6 patients were carefully analyzed to determine whether there was any relation between the length of the *P-R* interval and the acute exacerbations of the disease; no correlation could be drawn.

To determine the rôle of anoxemia in causing this abnormality, 4 of these 6 patients were given varying concentrations of oxygen, by the method described by Levy.¹⁵

The patients were given 100% oxygen for 20 minutes and 10% oxygen for 10 minutes; no excess CO₂ accumulated. Electrocardiograms, using Lead II, were taken at intervals of 3 to 5 minutes. All these patients showed similar changes: upon exposure to 100% oxygen, the *P-R* interval increased and the rate decreased; with 10% oxygen, which could be tolerated for only 8 to 10 minutes, the *P-R* interval decreased and the rate increased.

Atropine sulphate (2 to 3 mg.) intravenously caused an increase in rate and decrease in the *P-R* interval.

One hundred per cent oxygen did not appreciably alter the atropine effect, and atropine did not potentiate the effect of 10% oxygen in decreasing the *P-R* interval. Ten per cent oxygen seemed to potentiate the effect of atropine in decreasing the *P-R* interval, probably through the increase in heart rate. A typical protocol is shown in Table 2.

Three patients with sickle cell anemia with normal *P-R* intervals showed no conduction changes with the two concentrations of oxygen or with atropine, although similar changes in rate occurred.

One patient with rheumatic fever with no anemia and with an *A-V* conduction time of 0.22 had no change in rate or conduction with the different concentrations of oxygen, but with atropine the rate increased and the *P-R* interval decreased to 0.17.

Three patients with pernicious anemia in relapse were tested in the same way. The first had angina pectoris and a *P-R* interval of 0.21. One hundred per cent oxygen did not affect the conduction time, although the rate decreased slightly. Ten per cent oxygen for 11 minutes produced precordial pain, a moderate increase in rate, and an increase in the *P-R* interval to 0.22. The second patient showed changes in rate with the different concentrations of oxygen and with atropine, but the *A-V* conduction time did not vary. The third patient, who was in a very severe relapse, showed the same changes that occurred in the sickle cell anemia patients but the initial *P-R* value was normal and the changes were of less degree. This patient was too ill to test with atropine.

TABLE 2.—EFFECT OF OXYGEN AND ATROPINE ON RATE AND CONDUCTION IN SICKLE CELL ANEMIA (PATIENT L. H.).

	Rate.	P-R.
<i>First test. Control period</i>	88	.22
10% oxygen started.		
After 3 min.	97	.20
6 "	103	.18
8 "	105	.18-.19
100% oxygen started.		
After 3 min.	67	.23
5 "	67	.25
10 "	68	.26
15 "	66	.25
20 "	68	.25
<i>Second test. Control period</i>	75	.23
3 mg. atropine SO ₄ —I.V.		
After 1 min.	93	.21
2 "	91	.21
4 "	91	.20
6 "	91	.20
8 "	91	.20
10 "	91	.20-.21
13 "	91	.20
<i>Third test. Control period</i>	79	.23
100% oxygen started and 3 mg. atropine SO ₄ —I.V.		
After 3 min.	83	.21
6 "	86	.20
10 "	86	.20
15 "	81	.21
17 "	81	.20
10% oxygen started.		
After 2 min.	83	.21
4 "	97	.19
7 "	103	.18

One patient with severe acute anemia from malaria inoculata was tested shortly after the malaria was terminated. He had a bradycardia of 50 and a *P-R* interval of 0.15. One hundred per cent oxygen produced no change in rate or conduction, while 10% oxygen slightly increased the rate and the *P-R* interval.

Table 3 summarizes the changes that took place in the arterial blood of the patient whose protocol is given in Table 2.

TABLE 3.—EFFECT OF 100% AND 10% OXYGEN IN SICKLE CELL ANEMIA (PATIENT L. H.).

	Control resting fasting.	After 100% oxygen for 20 min.	After 10% oxygen for 10 min.
<i>P-R</i> interval	0.23	.25-.26	.18-.19
Rate	79.0	67.0	111.0
Oxygen content arterial blood, millimols/liter	3.87	4.90	2.22
Per cent saturation arterial blood	89.3	112.8*	51.2
CO ₂ content arterial blood, millimols/liter	24.6	24.3	23.6
Per cent sickled cells arterial blood	19.0	9.5	32.0
pH arterial blood	7.59	7.52	7.69
Serum sodium, m.eq./liter	136.0	136.2	135.2
Serum potassium, m.eq./liter	4.5	5.4	
Hemoglobin (Newcomer), gm./100 cc.	7.6	8.0	7.8
R.B.C., millions	2.72	2.84	2.72
Hematocrit, vol. % of packed R.B.C.	21.3	23.2	21.5

* Oxygen capacity of blood determined by saturating with room air.

Effect of 100% Oxygen. A marked increase occurred in the oxygen content of the arterial blood, while the CO_2 content and hydrogen-ion concentration did not change significantly. There was a marked decrease in the number of circulating sickle cells as determined by Sherman.²³ There was no alteration in the serum sodium or potassium and the values for hemoglobin, red blood cells, and hematocrit did not change significantly.

Effect of 10% Oxygen. As might be anticipated, there was a very marked decrease in the oxygen content and in the per cent saturation of the arterial blood. The CO_2 content and the hydrogen-ion concentration decreased slightly. The number of sickle cells increased markedly. The serum sodium and values for hemoglobin, red blood cells and hematocrit were not appreciably altered.

These results illustrate the marked anoxemia that these patients constantly suffer. They show that the anoxemia and *in vivo* sickling are increased when the *P-R* interval is shortened and the cardiac rate increased. When the anoxemia and *in vivo* sickling are decreased, the *P-R* interval is increased and the cardiac rate decreased. These findings are difficult to correlate in so far as cause and effect are concerned.

It is possible that the vagal tone is increased as part of the compensatory mechanism for the long-standing anemia. In support of this point of view is the fact that atropine, which temporarily blocks the vagus, has the same effect on rate and conduction as does a sudden increase in anoxemia.

Carotid sinus pressure had no effect in the above patient; it was not tried in other cases.

Pathologic-Anatomic Data. Eleven patients who had sickle cell anemia were examined postmortem. Only 4 were adults; the diagnosis of rheumatic heart disease had been made in 2 of these and questioned in 1 other. Her case history is presented in some detail.

CASE 2.—H. B. (Unit No. 135000, Patient 11, Table 4). This 28-year-old negress was first seen in this hospital in 1930 at the age of 18, complaining of weakness. She had always suffered poor health and for many years had had frequent attacks of polyarthritis. These usually occurred in the winter in association with sore throats and were accompanied by jaundice. At 15, she had apparently. Examination showed a poorly nourished, pallor and jaundice. The temperature was 101° . Blood pressure 125/80. The heart was enlarged to right and left, and Roentgen ray showed a prominent pulmonary conus. The sounds were rapid, regular and loud with marked accentuation of P_2 . There was a loud systolic murmur over the whole precordium and at the apex, a third heart sound and an indefinite presystolic rumble. The liver was enlarged. The lungs were clear and there was no edema. Laboratory examinations showed a severe sickle cell anemia which persisted throughout the next 10 years, and evidence of chronic nephritis. Electrocardiogram was normal.

A few months later, she was admitted again because of epigastric pain, nausea, and vomiting. While under observation, she had a "crisis" with generalized bone pain which was followed by transient swelling over both ulnæ.

She then felt quite well until the age of 24 when she first noticed exertional dyspnea and ankle edema. One year later, she became pregnant and her symptoms became so severe that an abdominal hysterotomy was done. At this time, the late diastolic rumble was more definite. Kidney function was markedly impaired with some azotemia.

TABLE 4.—PATHOLOGIC DATA IN SICKLE CELL ANEMIA.

Case No.	Age.	Sex.	Average normal heart weight (gm.).	Actual heart weight (gm.).	Per cent increase.	Remarks.
1. A. P.	2	M	60	90	50	Cardiac failure during crisis 1 year before death; died of pneumococcal meningitis.
2. A. C.	2	F	56	70	25	Died in crisis.
3. M. B.	2	F	56	110	96	Died of bronchopneumonia.
4. J. S.	3	M	65	125	92	Died in crisis.
5. T. H.	3	M	65	95	46	Died in crisis.
6. C. S.	5	M	85	150	76	Died in crisis.
7. D. S.	6	F	94	140	48	Died of cirrhosis of liver.
8. P. S.	15	F	200	280	40	Clinical diagnosis of rheumatic heart disease; died in crisis.
9. J. J.	22	M	300	440	47	Died in uremia, heart failure; cirrhosis of liver.
10. W. B.	24	M	310	480	55	Clinical diagnosis of rheumatic heart disease; died in uremia, heart failure.
11. H. B.	28	F	270	460	70	Died in uremia, heart failure.

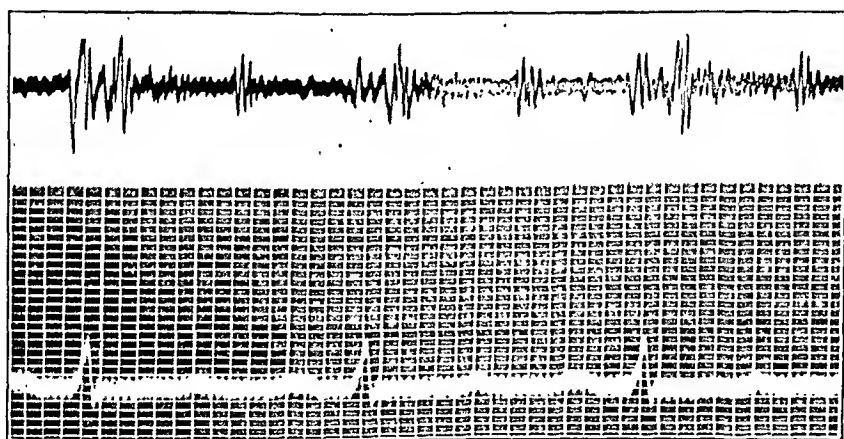


FIG. 6.—Stethocardiogram (H. B., Table 4) showing loud presystolic element, systolic murmur, and third heart sound.

She worked as a housekeeper for the next year and felt remarkably well. The dyspnea, edema, weakness and epigastric pain returned, however, and one year before death, she was again admitted to the hospital with definite evidence of cardiac failure. Blood pressure 170/85. The cardiac signs remained as before but there was edema, pulmonary congestion, elevation

of venous pressure, and hepatomegaly. The signs of heart failure improved very slowly on bed rest and digitalis, and blood pressure fell to normal, but the non-protein nitrogen slowly rose and renal function grew progressively worse.

She continued to take digitalis after discharge but heart failure returned, and 4 months before death she was once more admitted. Blood pressure 150/80. The heart had further increased in size, and the signs were much as before. Figure 6 shows the loud presystolic sound that was present. This was interpreted by some as a murmur, by others as a gallop.

She was admitted for the last time in January, 1940, suffering with severe congestive heart failure, uremia, and slight hypertension, 160/75. She died after 3 days with terminal pneumonia.

Anatomic Diagnosis (Dr. R. Follis). Sick cell anemia with extreme fibrosis and shrinkage of spleen. Chronic glomerulonephritis. Hemosiderin in kidneys. Cardiac hypertrophy and dilatation. Myocardial scars, slight. Hydropericardium. Lobular pneumonia. Chronic cholecystitis, with cholelithiasis.

The heart was enlarged in every case (Table 4). The estimated normal weights are obtained from the tables of Coppoletta and Wolbach⁷ and Roessle and Roulet.²² The cardiac hypertrophy was diffuse in all cases.

The endocardial surfaces and valves were normal in every case. There was moderate dilatation of the pulmonic orifice in several instances. In Patient 11, where the pulmonic conus was prominent on Roentgen ray, the ring was definitely dilated. The pericardial surfaces were always normal. Except for some hypertrophy of the muscle fibers, the myocardium showed no constant changes. No Aschoff bodies were found.

The lungs showed edema in more than half the cases and bronchopneumonia in several. No case showed any such striking changes in the pulmonary vascular tree as described by Yater and Hansmann.²⁹

The liver was uniformly enlarged, except in the 2 patients who had cirrhosis. There was usually mild chronic passive congestion with deposition of pigment and occasionally central necrosis.

The kidneys uniformly contained large deposits of hemosiderin in the convoluted tubules. There was a far-advanced nephritis in 2 patients, glomerulonephritis in Case 11 and a peculiar nephritis of undetermined type in Case 9. In Patients 5 and 8, there was slight scarring of the cortex.

Discussion. Cardiac hypertrophy due to anemia has been produced experimentally in dogs by Lüdke and Schüller.¹⁹ Cardiac enlargement in pernicious anemia has frequently been noted clinically and at autopsy; and these patients may also have physical signs strongly suggesting valvular disease.

In 1931, Ball² reported the first case in which Roentgen ray evidence of cardiac enlargement in a young woman with hypochromic microcytic anemia disappeared after 3 months as the anemia re-

sponded to treatment. The patient also had the physical signs of mitral stenosis and these likewise disappeared.

Gunewardene¹⁰ has reported several cases of chronic hookworm anemia with cardiac enlargement, systolic and diastolic murmurs at apex and base, and mild congestive failure. As the anemia improved, the unusual cardiac signs disappeared. Only 1 patient died; the heart in this case was found to be hypertrophied and dilated, with normal valves and endocardium.

In 1937, Porter²⁰ carefully studied cardiac function in severe hookworm anemia and found cardiac enlargement, confirmed by Roentgen ray examination, with systolic murmurs. The heart rate and blood pressure were normal in the adults, and congestive heart failure was not a prominent feature. Venous pressure and circulation time were normal and the vital capacity was not reduced. Electrocardiograms were normal except in one 23-year-old woman who had a *P-R* interval of 0.21. Unfortunately a record was not obtained after improvement had taken place. In the majority of cases, the heart decreased in size as the anemia improved. The other cases showed no decrease by Roentgen ray examination, but they were followed for only 6 to 8 weeks and it seems probable that all the hearts would have decreased in size had the patients been followed for a longer period.

Thus it is apparent that any severe anemia of sufficient duration may be responsible for the cardiac signs that are present in sickle cell anemia. The signs are probably more pronounced and more frequent in sickle cell anemia because of its chronicity and resistance to treatment.

Records of 2 cases of chronic hemolytic jaundice, which may closely resemble sickle cell anemia, were found in the files of our Pathological Department. Both had enlarged hearts, with systolic and diastolic murmurs, and at autopsy showed cardiac hypertrophy with normal valves and endocardium.

A late diastolic murmur at the apex has been noted in other conditions in which the mitral valve was later found to be normal. Wood and White²⁷ mention its presence in 4 patients with diffusely enlarged hearts, while Wyckoff and Bunim²⁸ note its occurrence in cor pulmonale. Bland, White and Jones⁴ discuss the significance of a presystolic apical murmur in 32 patients with acute rheumatic carditis. None of these had cardiac murmurs when examined 8 years later. These authors suggest that myocardial weakness and ventricular dilatation create a "relative mitral stenosis" when the mitral ring does not stretch as much as the ventricle dilates. The same conditions could account as well for the presystolic murmur that is present in sickle cell anemia.

In 1937, Bartels³ reported a case of severe congestive heart failure in a 76-year-old white male who had a severe chronic posthemor-

rhagic anemia from a bleeding peptic ulcer. The patient made a rapid recovery when treated at rest with salyrgan and iron. No digitalis was ever administered, and several years later there was no evidence of myocardial insufficiency.

Congestive heart failure has not so far occurred in any of the living patients, although they probably have a diminished cardiac reserve which is not detectable by the methods used to study cardiac function. In the terminal stages, however, congestive heart failure commonly occurs.

The crises of sickle cell anemia closely mimic episodes of acute rheumatic fever with joint pains, fever, leukocytosis, cardiac enlargement and murmurs, and a prolonged *P-R* interval. The presence of anemia and jaundice in a negro with these findings should suggest to the physician that he examine the blood carefully. There are, however, two important points in which these crises differ from rheumatic fever: *first*, the history or presence of pain over the long bones as well as in the joints, and *second*, the failure to respond to salicylates.

Treatment. There is no specific or effective treatment for the anemia. Transfusions need not be given unless the patient is having a hemolytic crisis. These patients frequently have severe transfusion reactions and the benefit derived from transfusion is of short duration.

Digitalis has been of no aid in treating the congestive failure that occurs in the late stages of the disease, or during a hemolytic crisis. One child who had congestive failure during a severe hemolytic crisis one year before death, received digitalis to the point of intoxication without any improvement. His recovery from myocardial failure occurred promptly when the crisis had ended.

The recurrent leg ulcers are extremely difficult to heal. Adequate rest with elevation of the legs prevents the edema which usually precedes the ulcers. Variable results have been obtained by local excision, followed by grafting, and mecholyl iontophoresis. Lumbar sympathectomy has produced good results in 1 case.

Summary. 1. The heart is diffusely enlarged in patients with sickle cell anemia. There are usually systolic and diastolic murmurs and a third heart sound at the apex, and an accentuated second pulmonic sound with a systolic murmur at the base.

2. The *P-R* interval of the electrocardiogram is often prolonged.

3. The similarities between rheumatic fever and sickle cell anemia are discussed. In sickle cell anemia, pain is not confined to the joints and the response to salicylates is not striking.

4. Although the diagnosis of rheumatic heart disease has often been made in patients with sickle cell anemia, it has not yet been confirmed at autopsy.

5. Congestive heart failure, not responding to digitalis, is common only in the terminal stages of the disease.

6. The cardiac changes in sickle cell anemia are probably secondary to the severe long-standing anemia.

Conclusions. 1. No cause other than the profound anemia is found to explain the cardiac changes in patients with sickle cell anemia. The mechanism by which any anemia produces changes in the heart is not entirely understood, but it seems probable that the hypertrophy and dilatation are compensatory for the prolonged anoxemia.

2. The cardiac changes of patients with sickle cell anemia are more marked than the changes found in other anemias. This is because sickle cell anemia is somewhat unique in the long duration of such a severe degree of anemia.

3. The prolonged $A-V$ conduction time is probably due to increased vagal tone, which also appears to be secondary to, or compensatory for, the prolonged anoxemia.

4. Although the clinical picture may closely resemble rheumatic fever, there is no proved instance of the two diseases occurring together. From the available data, there is no need to regard these patients as uncommonly liable to rheumatic fever.

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A NOTE ON CARDIAC MURMURS.

RECOMMENDATION FOR A REVISED TERMINOLOGY.

BY PAUL D. WHITE, M.D.,

AND

F. DENNETTE ADAMS, M.D.,

BOSTON, MASS.,

AND

DONALD CRAIB, M.D.,

JOHANNESBURG, SOUTH AFRICA.

SEVERAL years ago it became apparent to us that the present classification of heart murmurs as *functional* and *organic* was not only unsatisfactory but confusing. The term *functional* is applied loosely to two distinct groups of murmurs: those found in the normal person and unaccounted for by the presence of cardiovascular or other disease, and those produced by pathologic dilatation of a valve ring, great vessel, or heart chamber. The same term, therefore, has for years been used to describe, on the one hand, a murmur of no clinical importance, and on the other, a murmur which may have serious implications.

The term *organic* is similarly unsatisfactory; as used today, it refers only to the murmurs caused by actual deformity of a valve. Yet serious organic disease of the heart muscle resulting in cardiac dilatation may in the absence of valve deformity cause a murmur. In infarction of the heart, for example, a systolic murmur due to mitral regurgitation is common, yet no valve deformity exists. To call this murmur functional conveys the erroneous impression that it has no serious import.

The terms "inorganic" and "accidental" are likewise unsatisfactory because of their inexact and vague connotation.

The true nature of the various types of murmurs is in our estimation more clearly indicated by the following nomenclature:

Physiologic Murmurs. A. Intracardiac or intravascular. B. Extracardiac. (a) Cardiopulmonary. (b) Pericardial.

Pathologic Murmurs. A. Due to structural valvular disease. B. Due to congenital cardiovascular defects. C. Due to dilatation of ventricles or aorta or pulmonary artery from: (a) Cardiovascular disease. (b) Other diseases, such as anemia, thyrotoxicosis, or severe infection. D. Due to pericarditis.

I. Physiologic Murmurs. These are frequently found in normal persons and may be intra- or extracardiac in origin.

A. *Intracardiac or Intravascular.* Almost all of these murmurs are systolic in time. They are most often heard over the pulmonic valve area, and the majority of the remainder are at the apex. They are usually short, rarely occupying all of systole, are soft and blow-

ing in quality, and are heard over a limited area. They are not associated with cardiac enlargement or any other evidence of heart disease. They may be louder at the end of inspiration but much more often at the end of expiration. They are likely to be evanescent or inconstant. They may appear after hard exertion and disappear within a few minutes or hours. They vary with the position of the body, being loudest as a rule in recumbency and often are heard only in that position.

B. *Extracardiac*. (a) Cardiopulmonary murmurs (short for murmurs within the lungs produced by the action of the heart). The term currently used to describe these murmurs, *cardiorespiratory*, should be abandoned because of its ambiguity; it is applied not only to murmurs arising in the lung—the true cardiopulmonary murmurs—but is also incorrectly applied to intracardiac or intravascular murmurs which happen to be heard more clearly in one phase of respiration (usually expiration) than in the other. Cardiopulmonary murmurs are usually systolic in time, rarely diastolic, they are blowing in quality, and relatively faint. They are thought to be the result of cardiac action on the lungs themselves in squeezing air from a small portion of the lung overlying the heart by compression and of drawing air into the lung adjacent to the heart by suction. Since both vary with respiration, it is sometimes difficult to differentiate true cardiopulmonary murmurs from physiologic murmurs of intracardiac or intravascular origin. (b) Pericardial sounds. Superficial scratchy sounds of short duration, systolic or diastolic or both, are occasionally heard along the left border of the sternum, particularly after exertion or under other circumstances of increased blood flow, as in thyrotoxicosis. They can probably be explained as due to compression of the pericardial surfaces by the vigorously acting heart or pulmonary artery. Ortiz has demonstrated that pericardial friction sounds can be produced by pressure on a normal pericardial surface.*

II. *Pathologic Murmurs*. These are systolic or diastolic and can be divided into three categories:

- A. Those due to structural disease of the valves.
- B. Those due to congenital cardiovascular defects.
- C. Those found with dilatation of a vessel or chamber secondary to: (a) Cardiovascular disease, such as the apical systolic murmur of relative mitral insufficiency in a case of hypertension with pronounced left ventricular enlargement, or of rheumatic myocarditis, or of myocardial infarction. (b) Other disorders which secondarily affect the circulatory system, such as anemia.

D. Those due to acute pericarditis. These are systolic or systolic and diastolic in time, often scratchy, and usually best heard at the left lower border of the sternum or midway between that region and the apex. They may be designated simply as friction sounds.

* Ortiz y Ramirez, T.: Arch. latino am. de cardiol. y hemat., 3, 45, 1933.

It is often difficult, indeed impossible, to decide whether a systolic murmur, when it is slight in degree, is physiologic or pathologic. Likewise, it is sometimes impossible to determine in the case of pathologic murmurs whether or not they are due to deformed valves. Moreover, both valvular deformity and dilatation of heart chambers or great vessels may be factors in the same case. Nevertheless this simple classification is one we have found to be far superior to the old one, and we recommend its adoption.

As examples of the use of this revised nomenclature of heart murmurs, we present an analysis of two groups of cases: (1) 100 Harvard freshmen (among the first 526 examined in 1939-40) who showed murmurs;* (2) 100 private patients.†

	Physiologic.		Pathologic.‡			
			Due to dilatation.		Due to valvular deformity.	
<i>Systolic.</i>	Students.*	Patients.†	Students.*	Patients.†	Students.*	Patients.†
Pulmonic or basal	44	12	0	1	0	0
Apical	33	6	0	17‡	1§	22‡
Aortic	3	3	0	9	0	4
Left border alone	8	0	0	0	0	1
Apex and base	7	1	0	10‡	0	2‡
Precoordial	4	2	0	1	0	0
<i>Diastolic alone.</i>						
Apex	0	0	0	0	0	2
Base	0	0	0	1	0	2
Apex and base	0	0	0	0	0	1
Total	99	24	0	39	1	37

* Courtesy of Dr. Arlie V. Boek, Professor of Hygiene, Harvard University.

† Records of Dr. Paul D. White.

‡ Undoubtedly in several cases both dilatation and valvular deformity were responsible factors.

§ This case showed also diastolic murmurs, mitral and aortic.

¶ Of these 29 cases, 27 showed also diastolic murmurs, mitral, aortic, or both.

THE EARLY DIAGNOSIS OF SYPHILITIC AORTITIS.*

By S. BOHARAS, M.D.,

SENIOR ASSISTANT IN MEDICINE,

LESTER HOLLANDER, M.D.,

CHIEF, DEPARTMENT OF DERMATOLOGY AND SYPHILOLOGY,

AND

MAURICE GOLDSMITH, M.D.,

CHIEF, DEPARTMENT OF RADIOLOGY,
PITTSBURGH, PA.

(From the Department of Syphilology, Montefiore Hospital.)

SYPHILIS is an important cause of heart disease that usually appears 15 to 20 years after the primary lesion. During the long

* This study was aided through a grant from the Isaac Kaufman Foundation, Montefiore Hospital.

latent period few cases with early syphilitic aortitis are recognized. In the majority of instances the diagnosis is made late in the disease when serious complications of aortitis are present, namely, aortic regurgitation, saccular aneurysm or stenosis of the coronary ostia.

The diagnosis at this late stage of the disease is of little value. Because the results of antisyphilitic treatment are dependent upon the stage of the disease in which it is started,^{14a,28} it is very important that aortitis is recognized before complications develop. Early diagnosis, however, is very difficult. Many writers^{3,7,31} recognize this although contrary views^{10,15,17,18} are to be found. The purpose of this paper is to determine the feasibility of the diagnosis of early or uncomplicated syphilitic aortitis.

Material and Methods. The material used consisted of 200 syphilitic patients without saccular aneurysm, arterial hypertension or valvular disease and 200 individuals of the same age and sex without syphilis, this latter group being used as a control. The diagnosis of syphilis was based on the presence of repeated positive Wassermann and Kahn reactions of the blood. In the control group, syphilis was excluded by history, physical examination, which included neurologic examination, and repeated serologic investigation of the blood.

The study was limited to patients between 20 and 50 years of age free from roentgenographic and physical evidence of arteriosclerosis. Patients with abnormal elevation of the diaphragm or kyphoscoliosis were excluded from the study. Patients with past or present arterial hypertension and rheumatic aortic insufficiency were also excluded since dynamic dilatation has been reported in each of these conditions.²²

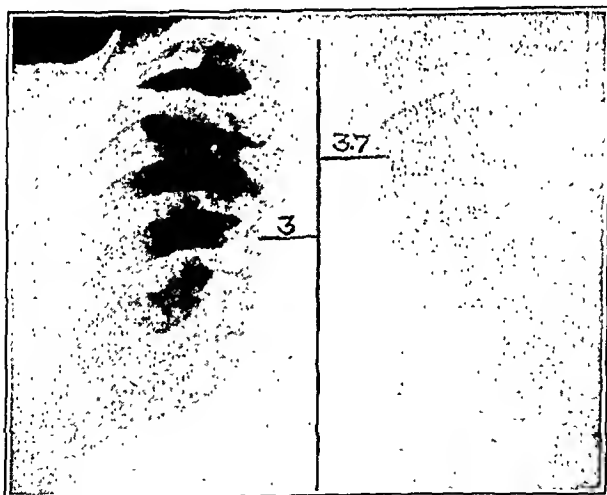


Fig. 1.—Vaquez-Bordet measurement of the aortic arch.

The following procedures were obtained in each patient: 1, a teleroentgenogram and fluoroscopy; 2, a physical examination; and 3, an electrocardiogram. The roentgenograms were obtained in the postero-anterior and left anterior oblique positions, the latter at an angle of about 45 degrees. These were taken at the end of moderate inspiration, at a distance of 6 feet, with the patient standing. Physical examination was conducted in the

sitting position. The standard as well as the chest leads were used in obtaining the electrocardiograms. In the chest lead the right arm electrode was placed over the apex of the heart and the indifferent electrode on the left leg.

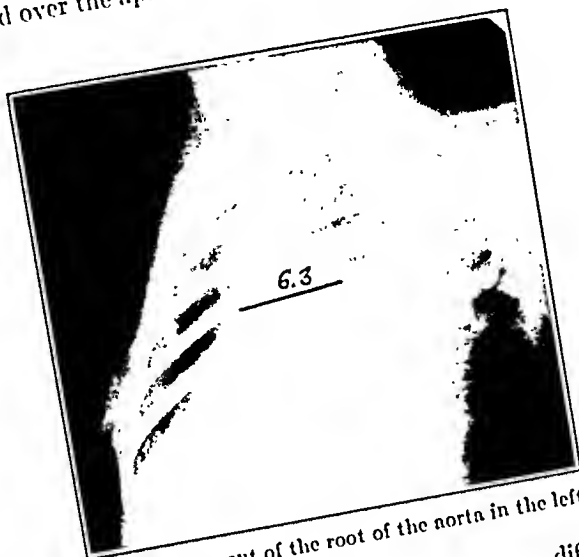


FIG. 2.—Hampton's measurement of the root of the aorta in the left oblique position.

The aortic arch and root were measured by three different methods: 1, Vaquez-Bordet³⁰; 2, Hampton¹⁶; and 3, Fray.⁹ These methods were studied since they have been suggested as means of recognizing syphilitic

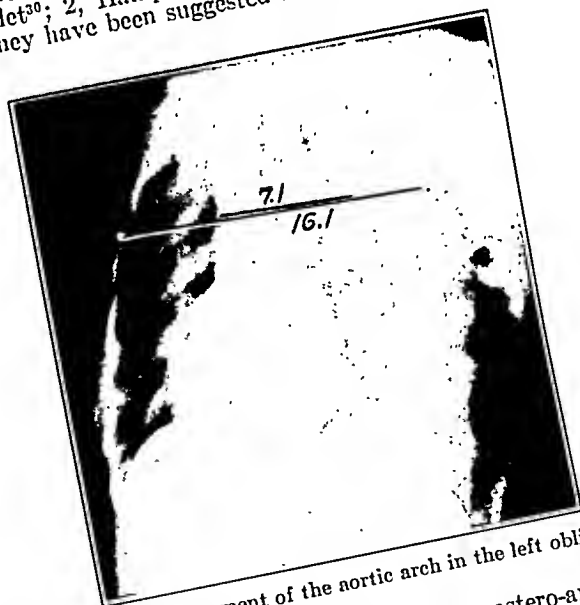


FIG. 3.—Fray's measurement of the aortic arch in the left oblique position.

aortitis. The width of the aortic shadow in the postero-anterior teleroentgenogram was obtained "by adding the measurement of the farthest point of the ascending aorta to the right of the mid-sternal line to the measure-

ment of the farthest point of the aortic knob to the left of the mid-sternal line"³⁰ (Fig. 1). The width of the root of the aorta in the left oblique position was obtained by drawing a transverse line from the "junction of the ascending aorta with the anterior border of the heart to the region of the pulmonary artery where it intersects the posterior border of the heart"¹⁰ (Fig. 2). The aortic arch was also measured in the left oblique position in the manner indicated by Fray.⁹ "A line was drawn transversely from the ascending limb of the arch to a corresponding point on the descending limb at this level. The chest measurement was taken at the level of the arch measuring from the right anterior chest wall to the left costovertebral articulation. The diameter of the chest was divided by the diameter of the arch to obtain a ratio called the transverse-arch-chest index" (Fig. 3).

Results. I. *Roentgen Examination.* (A) An analysis of the Vaquez-Bordet measurement in 200 normal patients revealed a wide variation in the size of the normal aorta. The latter measured 3.9 to 7.8 cm. No definite relation could be demonstrated between the size of the aorta and the race, sex, height, weight, chest diameter, occupation and age of the individual patient, although there was a tendency to an increase in the size of the aorta in obese or older patients. It is impossible to determine a standard of normal measurement on account of the marked variability of the normal aorta.

A summary and comparison of the Vaquez-Bordet measurement of 200 non-syphilitic and 200 syphilitic patients by age groups is shown in Table 1. The impressive feature of this comparison is that, with a few exceptions, the two groups present identical measurements. The increase in the size of the aorta is virtually the same with advancing years in syphilitic and non-syphilitic patients and is apparently due to arteriosclerosis.

TABLE 1.—A COMPARISON OF THE VAQUEZ-BORDET MEASUREMENT IN NORMAL AND SYPHILITIC SUBJECTS.

Age.	Extreme variations of aortic width (cm.).	Average aortic width (cm.).
20-30	3.9—6.6	5.0
20-30	3.2—6.7	5.0
31-40	4.8—7.6	5.8
31-40	4.6—7.5	5.8
41-50	4.7—7.4	6.2
41-50	4.8—10.0	6.7

Black—normal. Italic—syphilitic.

An analysis of the syphilitic group revealed the fact that 3% had unequivocal or diffuse aneurysmal dilatation of the thoracic aorta. The aortic shadow then has a characteristic fusiform or spindle-shaped appearance in the postero-anterior and oblique positions (Fig. 4). It is important to note that the roentgenologic diagnosis of syphilitic aortitis in these instances was made late in the disease, 18 to 20 years after the onset of the infection. Thus, it appears that the postero-anterior teleroentgenogram is of practically no aid in the early diagnosis of syphilitic aortitis but of distinct value in the late stages when wide dilatation of the aorta exists, since in

many instances it is the first or even the only sign to lead one to the proper diagnosis. Before making the diagnosis of diffuse aortic dilatation, however, the postero-anterior view must be supplemented by an oblique view for accurate diagnosis.²⁴ Otherwise, elongation and tortuosity of the aorta of sclerotic origin may be interpreted incorrectly as dilatation.

We attempted to determine the influence of arterial hypertension or advanced arteriosclerosis upon the width of the aortic arch. For this reason we studied a number of non-syphilitic patients between 40 and 50 years with hypertension as well as another group of patients between 50 and 70 years, with and without hypertension. We found, like other workers,²³ that wide aortic dilatation may exist with arterial hypertension or advanced arteriosclerosis. The result



FIG. 4.—Postero-anterior and left oblique teleroentgenogram illustrating diffuse dilatation of the aorta.

is that in the complicating presence of these conditions it is impossible to recognize syphilitic aortitis by Roentgen ray before the advent of saccular aneurysm.

B. Hampton's¹⁰ method of measuring the root of the aorta seems to be of little value in the early diagnosis of syphilitic aortitis. The root of the normal aorta measured 4 to 7.4 cm. This wide variation is responsible for the difficulty in obtaining a reliable standard of normal measurement.

Hampton's measurement fails to distinguish the syphilitic from the non-syphilitic aorta prior to the onset of marked aortic dilatation. A summary and comparison of the root measurement of Hampton in syphilitic and non-syphilitic individuals by age groups is presented in Table 2. With a few exceptions, the two groups present similar measurements. In our study the maximum root

measurement in a normal patient was 7.4 cm. rather than 6 cm. as reported by Hampton. Among 200 syphilitic patients without complications, only 2 cases (1%) presented root measurements above 7.4 cm. These cases had wide dilatation, recognized first by Roentgen ray 20 years after the primary infection.

TABLE 2.—A COMPARISON OF THE ROOT MEASUREMENT OF HAMPTON IN SYPHILITIC AND NON-SYPHILITIC SUBJECTS.

Age.	Extreme variations of aortic root (cm.).	Average aortic root (cm.).
20-30	4.0—6.2	5.18
20-30	<i>3.5—6.5</i>	<i>5.1</i>
31-40	4.0—7.0	5.5
31-40	<i>4.0—7.0</i>	<i>5.4</i>
41-50	4.0—7.4	5.6
41-50	<i>3.0—10.0</i>	<i>6.4</i>

Black—normal. Italic—syphilitic.

Seven and a half per cent of normal and 14% of syphilitic individuals presented root measurements between 6.2 and 7.4 cm. The increased incidence among syphilitics is no doubt significant since syphilis commonly involves the root or proximal portion of the aorta. But it is impossible to evaluate this fact clinically since Hampton's measurement fails to differentiate the syphilitic from the non-syphilitic aorta.

C. Fray⁹ concluded from his studies of the aortic arch that the transverse-arch-chest index sharply differentiates the normal from the abnormal aorta. He found that the normal arch had a transverse-arch-chest index above 1.9 and that the pathologic or dilated aorta had a transverse-arch-chest index below 1.9.

Our findings indicate that Fray's index is of little value in the early diagnosis of syphilitic aortitis. We found: 1, that normal patients may have an index below 1.9; and 2, that the indices of normal patients were indistinguishable from those of syphilitic patients prior to the development of marked aortic dilatation. A summary and comparison of the indices by age group may be seen in Table 3. The lowest index in our normal group was 1.65 and occurred in a male of 35. Only 1 out of 200 syphilitic patients had an index below 1.65.

TABLE 3.—A COMPARISON OF THE TRANSVERSE-ARCH-INDEX OF FRAY IN NORMAL AND SYPHILITIC SUBJECTS.

Age.	Extreme variations of transverse-arch-index (cm.).	Average transverse-arch- index (cm.)
20-29	1.65—2.93	2.36
20-29	<i>1.75—2.75</i>	<i>2.33</i>
30-39	1.80—3.15	2.14
30-39	<i>1.65—3.15</i>	<i>2.31</i>
40-49	1.71—2.59	2.15
40-49	<i>1.55—2.32</i>	<i>2.03</i>

Black—normal. Italic—syphilitic.

Of the normal group 2.7% and of the syphilitic group 7% had an index below 1.9. The increased incidence may mean syphilitic aortic disease but it is difficult to evaluate this clinically.

D. Fluoroscopy has been suggested as an aid in the diagnosis of aortic syphilis. Local dilatation with increased pulsation or increased density and irregularity of the aortic wall have been regarded diagnostic of syphilitic aortitis by various observers.^{15,26}

Our results with fluoroscopy have led us to believe that these signs are not pathognomonic of syphilitic aortitis. Two cases of local dilatation of the proximal portion of the aorta were observed; one in a syphilitic, the other in a non-syphilitic. O'Kane and his coworkers²⁰ observed local aortic dilatation in a few patients that proved to be due to arteriosclerosis at autopsy. This lesion has also been described in arterial hypertension, coarctation of the aorta, rheumatic aortic insufficiency and syphilitic aortitis.¹⁹ In other words, it must be remembered that local aortic dilatation is suggestive but not pathognomonic of syphilitic aortitis. We missed the correct diagnosis in one instance because we failed to take this into consideration. This patient had a positive Wassermann reaction, signs of aortic insufficiency and Roentgen ray evidence of local dilatation of the aorta suggestive of beginning aneurysm. Autopsy, however, revealed a rheumatic lesion of the aortic and mitral valves and a normal aorta.

Our failure to identify early syphilitic aortitis roentgenographically has been noted previously by other authors.^{1,14b} Various proposed measurements of the aorta to detect early syphilitic aortitis have proved to be unreliable ground for diagnosis leading to error.

Every reported radiologic abnormality of the syphilitic aorta including saccular aneurysm has been observed in non-syphilitic aortic disease. Although saccular aneurysm of the aorta is almost always the result of syphilis, it must be remembered that in rare instances this lesion may be due to advanced arteriosclerosis, particularly in aged individuals. In our study of 200 normal patients diffuse dilatation was not observed in a single case. In 200 syphilitic patients of approximately the same age diffuse aneurysmal dilatation occurred in 6 cases or in 3% of the series. Diffuse dilatation was also observed in a few non-syphilitic cases, but always in the presence of marked hypertension; rheumatic aortic insufficiency or in aged patients with obvious arteriosclerosis. Evidently, diffuse dilatation is the most reliable Roentgen ray sign of syphilitic infection of the aorta before the advent of saccular aneurysm, providing arterial hypertension, arteriosclerosis and rheumatic aortic insufficiency are first ruled out.

Since the roentgenologic diagnosis is largely dependent upon a marked increase in the size of the aorta, lesser degrees of aortitis are frequently unrecognized. In fact, one serious complication of aortitis may be present without any change in the size of the aorta, namely, stenosis or occlusion of the coronary ostia.²⁷

II. Physical Examination. Increased pulsation in the supra-sternal notch, a systolic aortic blow, an accentuated or tympanitic aortic second sound and retromanubrial dullness have been reported as signs of syphilitic aortitis. The presence or absence of each of these signs was noted by us in the physical examination of 200 syphilitic and 750 non-syphilitic patients with the aim of determining their value in the diagnosis of syphilitic aortitis.

A. The least reliable of all physical signs proved to be visible or palpable pulsation in the suprasternal notch. Prominent pulsation was present in 2 out of 6 cases with diffuse aortic dilatation and slight or absent in 4. The diminished pulsation of the diseased aorta has been observed by other workers.²⁶ On the other hand, we frequently obtained prominent pulsation in both syphilitic and non-syphilitic patients who showed no evidence of dilatation on roentgenologic examination.

B. Retromanubrial dullness proved to be of little value in the diagnosis of aortitis. We obtained this sign in many non-syphilitic patients, with and without arterial hypertension. In some of these cases the aorta proved to be dilated on Roentgen examination; others however were merely elongated.

The "silent" aneurysm without signs or symptoms is well known to clinicians. Of 6 cases of saccular aneurysm seen in the course of this study one was suspected on the basis of percussion; while 5 remained undiagnosed after physical examination. Kampmeier¹² recently analyzed the results of percussion in 566 cases of saccular aneurysm. He found abnormal dullness in 22.4% of the cases and absent in the remainder. Obviously, percussion is not a very reliable method of clinical diagnosis since abnormal dullness is often absent in the presence of a dilated aorta and present more frequently with arteriosclerosis or hypertension than with aortic syphilis.

C. A slight systolic aortic murmur occurred in 3 out of 200 syphilitic patients or in 1.5% of the series. Two of these had diffuse aneurysmal dilatation of the aorta, one a normal aorta. It is important to note that a systolic aortic murmur occurred in only 2 out of 6 syphilitic patients who presented diffuse aortic dilatation; 4 had normal heart sounds. Furthermore, we obtained an identical murmur in 2% of the normal control series.

White and Wise³¹ have similarly pointed out that a loud aortic systolic murmur is not pathognomonic of aortic syphilis, but that it may occur with aortic dilatation not due to syphilis as well as with aortic stenosis of rheumatic or sclerotic origin. We agree with these observers that a systolic aortic murmur cannot be regarded as specific evidence of aortic syphilis.

D. The tympanitic aortic second sound has been regarded pathognomonic of aortic syphilis by some clinicians¹⁸ and of no value in diagnosis by others.³¹ (By a tympanitic or tambour aortic second sound is meant a change in the quality as well as an increase in the intensity of the heart sound, characterized by a hollow or drum-like sound.)

We believe that the tympanitic aortic second sound may be a clue to the correct diagnosis providing the general condition of the patient is carefully analyzed. We are certain that this sign may occur with arteriosclerosis or arterial hypertension as well as with syphilis. We obtained this sign in 5 (2.5%) of 200 syphilitic cases under 50 years of age without hypertension. On the other hand, this sign occurred only once in 500 normal cases of the same age period. Because this sign is rare in normal individuals⁴ we believe that it is of diagnostic value providing arteriosclerosis, valvular heart disease and hypertension are first ruled out. The following case illustrates this point.

Case Report. A colored male of 49 complained of moderate pain in the left axilla and left lower back, unrelated to effort. This was of 1 year's duration. Physical examination revealed a single positive physical finding, a tympanitic aortic second sound. In the absence of increased arterial pressure this sign suggested the possibility of aortic disease. The blood Wassermann reaction was negative, but questioning yielded a history of a primary infection 20 years ago. The roentgenogram revealed diffuse aortic dilatation (Fig. 4). The patient received a therapeutic test consisting of 4 gm. of potassium iodide daily and bismuth at weekly intervals. The response to the therapeutic test was dramatic. At the end of a month the pain was much less and the Wassermann and Kahn reactions of the blood became strongly positive on several occasions.

Although the tympanitic aortic second sound may be of value in diagnosis, this finding alone cannot be accepted as unequivocal evidence of aortic syphilis. Upon finding this sign, we believe that a careful roentgenologic examination is indicated to determine the presence or absence of an aortic lesion. In the final analysis, uncomplicated syphilitic aortitis can be recognized only by roentgenologic study since there are no physical signs that are pathognomonic of this condition.

III. Electrocardiograms. Electrocardiographic studies^{5,29} have failed to show any significant changes during or following the primary or secondary lesion, or any characteristic abnormalities in latent or tertiary syphilis.

We analyzed the electrocardiogram of 160 syphilitic patients. The interval between the chancre and the electrocardiographic study varied from 3 to 39 years with an average interval of 14.7 years.

The electrocardiogram rarely shows abnormalities in uncomplicated syphilitic aortitis. Of 160 syphilitic patients without demonstrable complications, 5 presented an abnormal tracing. These consisted of an absent Q_4 together with a positive T_4 , a diphasic T_2 , and a PR interval of 0.24 second respectively. It is well known that these changes are not pathognomonic of syphilitic aortitis. Six other syphilitic patients had an abnormal tracing, but chronic rheumatic heart disease was present in 1 and arterial hypertension in 5.

The electrocardiographic changes of cardiovascular syphilis de-

velop late in the disease and are relatively unimportant clinically. Such changes are generally due to aortic regurgitation or stenosis of the coronary orifice, and rarely, to gumma or myocarditis.¹¹ Changes in the ventricular complex were present in 5 out of 6 cases with aortic regurgitation in the present study.

A normal electrocardiogram, on the other hand, does not rule out cardiovascular syphilis. This occurred in 1 case with aortic regurgitation, in 3 patients with saccular aneurysm and in 3 patients with diffuse aortic dilatation.

In agreement with other workers³¹ we note that auricular fibrillation is rare in patients with syphilis. In our study auricular fibrillation occurred in 1 out of 200 syphilitic patients without aortic insufficiency, saccular aneurysm or arterial hypertension. It is significant that this patient had wide aortic dilatation and cardiac symptoms. Auricular fibrillation also occurred in 1 patient with aortic insufficiency and saccular aneurysm. A third case of auricular fibrillation was seen in association with syphilitic aortic insufficiency and hyperthyroidism. In this patient the arrhythmia subsided after a partial thyroidectomy. Evidently, auricular fibrillation is not only rare in patients with syphilis but, when present, is a manifestation of a cardiac complication, either syphilitic or non-syphilitic.

Discussion. In 1932 Moore, Dangle and Reisinger¹⁸ established diagnostic criteria for uncomplicated syphilitic aortitis. These criteria were: "(1) teleroentgenographic and fluoroscopic evidence of aortic dilatation; (2) increased retromanubrial dullness; (3) a history of circulatory embarrassment; (4) a tympanitic, bell-like accentuation of the aortic second sound; (5) progressive cardiac failure; (6) substernal pain; (7) paroxysmal dyspnea."

We are convinced that these criteria are not diagnostic of uncomplicated syphilitic aortitis, but are characteristic of aortitis with serious complications. It appears that Moore and his coworkers used the term uncomplicated aortitis inconclusively. By uncomplicated aortitis they understood a "supra-valvular involvement of the aortic wall with or without diffuse dilatation, but without valvular insufficiency or saccular aneurysm." It is significant that these workers failed to consider the condition of the coronary vessels in subjects with cardiac symptoms who came to autopsy. This is particularly important since a well-recognized cause of cardiac failure is syphilitic involvement of the coronary orifice. Stenosis or occlusion of the coronary orifice has been found at autopsy in 10% to 35% of cases with syphilitic aortitis.^{2,4,6,16,25} Careful pathologic studies have proved: 1, that uncomplicated syphilitic aortitis is symptomless; and 2, that cardiac symptoms in a syphilitic patient are due to complications of aortitis, *i. e.*, saccular aneurysm, valvular insufficiency or stenosis of the coronary orifice, or to some unrelated condition such as degenerative or rheumatic heart disease.^{13,32}

Cardiac symptoms, abnormal physical signs or a dilated aorta may occur with syphilitic aortitis but these criteria are not pathognomonic of this disease. It is well known that the identical criteria occur far more frequently with degenerative cardiovascular disease. The history of syphilis or the presence of a positive serology does not mean that syphilis is necessarily an etiologic factor. Furthermore, syphilitic aortitis and degenerative heart disease may co-exist with syphilis playing no rôle in the production of symptoms. Thus Perry and Langsam²¹ recently found at autopsy a number of cases with syphilitic aortitis who died of hypertensive disease. It cannot be emphasized too strongly that no single sign or symptom is all-important in the diagnosis of syphilitic aortitis. The diagnosis must rest upon roentgenologic examination plus a careful analysis of the general condition of the patient.

This study supports the contention that a positive clinical diagnosis of early syphilitic aortitis is practically impossible. This study clearly shows that a reliable diagnosis cannot be made before wide dilatation of the aorta has occurred. We agree with White and Wise²¹ that a positive diagnosis of cardiovascular syphilis can be made only when one or more of the following findings is present: 1, a saccular aneurysm of the aorta or innominate artery; 2, aortic regurgitation appearing for the first time in a middle-aged person with a positive serologic reaction for syphilis; or 3, a diffusely dilated aorta without aortic regurgitation or hypertension, past or present.

Summary. We have attempted to repeat previously emphasized methods of examination to determine their value in the diagnosis of early or uncomplicated syphilitic aortitis. Two hundred patients with syphilis and 200 patients as normal controls were used for this purpose. Our conclusions are as follows:

1. There is no single pathognomonic sign of early syphilitic aortitis discernible either by Roentgen ray, electrocardiogram or physical examination.
2. It is impossible at present to make a positive clinical diagnosis of early syphilitic aortitis.
3. Roentgen ray examination is a valuable aid in the diagnosis of late aortitis, at times being the first or only indication that such a condition exists.

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HISTOLOGIC KIDNEY CHANGES IN THE COMMON ACUTE INFECTIOUS DISEASES.

By MILTON KANNERSTEIN, M.D.*

PATHOLOGIST, ST. MARY'S HOSPITAL, CLARKSBURG, W. VA.

(From the Laboratory of Pathology, Willard Parker Hospital, New York, N. Y.)

THE physician, attending cases of the common acute infectious diseases, frequently experiences concern about the possibility of a renal complication, particularly in the presence of albuminuria and cylindruria. Discussions of the actual pathologic findings in the kidneys in these diseases have appeared in the medical literature over the course of many years, but are widely scattered under many individual subject headings. It was thought, therefore, that a review of the renal histopathology of the more common acute infectious diseases might be of interest. In this article no attempt is made to survey the extensive literature. Its basis is the postmortem material of 9 years (1930 through 1938) at the Willard Parker Hospital.

There was no selection of cases except that some were ruled out because of doubtful diagnosis or multiplicity of infection. There were 58 cases of scarlet fever, 70 cases of diphtheria, 98 cases of measles, 62 cases of pertussis, 16 cases of meningococcic meningitis, and 9 cases of varicella. The number of cases of poliomyelitis reviewed was arbitrarily limited to 50. In the text and the table included in this report the incidence of each type of lesion is expressed as a percentage of the total number of cases of that disease that came to autopsy. Because there were so few cases of influenzal

* Formerly Pathology Resident, Willard Parker Hospital, New York.

meningitis and varicella, the incidence was expressed as the absolute number of cases as well as percentage. The lesions are grouped as diffuse glomerular, tubular, interstitial and vascular.

TABLE I.—HISTOLOGIC CHANGES IN THE KIDNEYS IN THE ACUTE CONTAGIOUS DISEASES.

Disease.	Number of cases.	Diffuse glomerular lesions, %.		Tubular lesions, %.				Interstitial lesions, %.		Vascular lesions, %.				Clinical data, %.		
		Increased glomerular cellularity.	Glomerulonephritis.	Aluminous degeneration.	Hyaline degeneration.	Necrosis of tubular epithelium.	Casts in tubules.	Interstitial infiltration.	Interstitial edema.	Focal embolic glomerulonephritis.	Glomerular thrombi.	Septic embolism.	Aseptic embolism.	Albuminuria.	Positive blood cultures (all types).	Hemolytic streptococci in blood.
Scarlet fever	58	6	3.4	95	0	7	46	77	42	3.4	0	3.4	1.7	69	79	63
Diphtheria	70	7	0	91	25	16	67	48	13	1.4	4.3	2.8	1.1	93	50	48
Measles	98	3	0	93	8	4	36	19	7	0	3	0	0	81	73	60
Pertussis	62	0	0	77	19	0	5	1.6	0	0	6.4	0	0	67	33	13
Polio-myelitis	59	0	0	68	4	0	18	0	4	0	0	0	0	53	30	10
															(10 cases)	
Meningococcal meningitis	16	0	0	91	0	0	19	6.2	43	0	0	0	0	50	50	20
															(10 cases)	
Influenzal meningitis	10	0	0	70	10	0	50	30	20	0	0	0	0	87.5	37.5	0
														(8 cases)	(8 cases)	
Varicella	9	0	0	89	11	0	22	0	0	0	0	0	0	75	60	60
														(1 case)	(3 cases)	

GLOMERULAR LESIONS. Congestion of the glomeruli was very frequent. Droplets of protein matter were found in Bowman's capsule in most of those cases that showed degenerative tubular changes. Since the glomerular loops themselves were unchanged in these cases and there was no epithelial proliferation or desquamation, these changes were not regarded as inflammatory. Their incidence and significance appears to be about the same as toxic nephrotic changes, and they are not included in the table. The normal involutional obliteration and fibrosis of some glomeruli seen in infants and senile arteriosclerotic lesions were omitted as irrelevant.

The minimal glomerular lesion which may be regarded as inflammatory is listed as *increased glomerular cellularity*. Although this may be similar to the lesion referred to as "subclinical glomerulitis" by Bell,¹ no basement membrane staining was done nor any attempt made to distinguish between epithelium and endothelium, and we do not go beyond a descriptive term. This lesion is characterized by a marked increase in the cells of the wall of the glomerular tuft or in polymorphonuclears in the lumens of the loops. It will be noted from the table that these minimal glomerular lesions are infrequent.

A true *diffuse glomerulonephritis* was seen in only 2 cases of scarlet

fever (3.4% of the cases of that disease). In 1 case death occurred on the 28th day of the scarlet fever; in the other on the 22d day of the scarlet fever and the 12th day of the nephritis. The first showed swelling of all glomeruli which had anemic and very cellular loops filling the glomerular capsule. In numerous glomeruli of the second case the vascular tufts contained hyaline thrombi; epithelial crescents were present in many capsules; occasional small intracapsular hemorrhages were observed. Both cases had the clinical picture of glomerulonephritis.

TUBULAR LESIONS. *Albuminous degeneration* (also called granular degeneration, and from its gross appearance, cloudy swelling) was the most frequent lesion of any type in all the diseases dealt with. In the mildest cases it was seen in the proximal convoluted tubule, especially in the straight part situated in the medullary rays. In severe cases the entire proximal and distal convoluted tubules were involved. In the table all cases showing albuminous degeneration are listed whether it was seen alone or with the more severe degenerative changes. It was seen with almost equal frequency in scarlet fever, diphtheria, measles and meningococcic meningitis, and somewhat less frequently in pertussis and poliomyelitis. Albuminous degeneration alone, without the more severe forms of degeneration or the first stage of nephrosis (Fahr⁴), was observed in 80% of scarlet fever, 65% of diphtheria, 85% of measles, 58% of pertussis, 64% of poliomyelitis, and 94% of meningococcic meningitis.

The appearance of *hyaline droplets* indicates the second stage of nephrosis according to Fahr. In our series, hyaline droplet degeneration was never diffuse and was usually seen in the subcapsular and mid-cortical layers, often in the neck of the proximal convoluted tubule. In a few cases it was observed in the epithelium covering the glomeruli. The total of hyaline droplet degeneration seen, with or without tubular necrosis, as listed in the table, was highest in diphtheria with 25%. Pertussis came next with 19%. The incidence in measles, scarlet fever and poliomyelitis was low, with 8%, 9%, and 4% respectively. Hyaline droplet degeneration without necrosis, that is, the second stage of nephrosis, was 14% in diphtheria, 19% in pertussis, 5% in measles and 4% in poliomyelitis.

Coagulation necrosis, which indicates the third stage of nephrosis (Fahr), was seen most frequently in diphtheria where it was present in 16%. Far fewer cases of scarlet fever (7%) and measles (4%) showed this change. It was not present in the other diseases. Coagulation necrosis of an occasional single cell was not counted. Those cases alone were listed under this heading where groups of entire cross-sections of tubules showed deeply eosinophilic cells with pyknotic nuclei or absence of nuclei. In diphtheria desquamation of these deeply eosinophilic (necrotic) cells was often accompanied by regeneration of low slightly basophilic cells. The necrosis was usually limited to a few groups of tubules. In only 1 case was

necrosis diffuse, resembling that of mercurial poisoning. No calcium deposit as seen in mercury poisoning or in diphtheria of the pre-antitoxin days (Reiche⁶) was noted.

Casts. The presence of casts in the tubules as seen in histologic sections was enumerated. The findings are listed under tubular changes for reasons mentioned in the discussion. Casts, usually hyaline, were found with striking frequency in diphtheria (67%), and much less often even in scarlet fever, the disease which came next with 46%.



FIG. 1.—Scarlet fever. Interstitial infiltration (interstitial nephritis) (100 \times , slightly enlarged).

INTERSTITIAL LESIONS. These were an infiltration of inflammatory cells into the interstitial tissues and an inflammatory edema. They are listed separately, although both, probably, are parts of the same process (Kimmelstiel⁵).

The interstitial cellular exudate consisted chiefly of lymphocytes. Some large mononuclear and plasma cells were usually present. Small numbers of polymorphonuclears, including a few eosinophils, were found in scarlet fever. The infiltrates varied from small perivenous collections at the junction of the cortex and medulla to a diffuse, almost leukemoid, infiltration of both medulla and cortex.

Interstitial infiltration was seen most outstandingly in scarlet fever (77%) and in diphtheria (48%). In measles it was much less frequent (19%), and was negligible in other conditions.

The extent of the infiltration was estimated according to the scheme of Brody and Smith² wherein 1+ represents the perivascular collections; 2+ beginning infiltration into surrounding tissue, and 3+ and 4+ the more extensive and diffuse distribution. In scarlet fever 24% were of 3+ and 4+ degree; in diphtheria only 3% were of 3+ severity and none of 4+.

Interstitial edema, resulting in wider separation than normal, of the tubules in the cortex was also seen most commonly in scarlet fever (42%) where it was usually accompanied by interstitial cellular infiltration. It was less frequent in other diseases except in meningococcic meningitis where it was present in 43% of the relatively small series reviewed, with one-seventh of the cases showing cellular infiltration.

VASCULAR LESIONS (aside from diffuse inflammatory glomerular lesions). *Focal embolic glomerulonephritis* or glomerular embolism was seen in 2 cases of scarlet fever (3.4%) and 1 case of diphtheria (1.4%). These were septic emboli of a small number of glomeruli. The sepsis in 1 case of scarlet fever was the result of an acute hemolytic streptococcic ulcerative endocarditis; in the other, the organism was a pneumococcus, lobar pneumonia having followed the scarlet fever. In this case focal embolic glomerulonephritis was superimposed on diffuse glomerulonephritis which was present for a few days before the onset of the pneumonia. The two lesions were unmistakably different. In the diphtheria case blood culture failed to show any growth.

Thrombosis of otherwise unchanged glomerular loops was noted in a few cases of diphtheria, measles, and pertussis. There was no cardiac valvular or other lesion in these cases which might be a possible source of emboli. The thrombi consisted of fibrin without bacteria, the glomerular loops showed no necrosis or increased cellularity. No polymorphonuclears were seen in the capillaries or in the capsules; nor was any blood or epithelial crescent formation present in Bowman's capsules. The thrombosis affected a few or many glomeruli in one or both kidneys. Some of the kidneys showing this change were otherwise of surprisingly normal appearance and others showed degenerative changes in the tubules. In a few cases blood chemistry and urinalysis done shortly before death were found to be normal. Because of the negative findings these 9 cases could not be listed as focal glomerulonephritis. The cases occurred in children under 2 years of age. The significance or duration of the lesion could not be determined. They may be terminal.

Several cases of *embolic lesions*, either septic or aseptic, affecting renal blood vessels *other* than the glomerular tufts were seen in scarlet fever and in diphtheria. Aseptic embolism of the larger

branches of the renal artery arising from aseptic mural thrombi of the left ventricle was seen in a case of scarlet fever which presented also embolism of the popliteal artery, and in a case of diphtheria with embolism of the femoral artery and anemic infarcts of the spleen. Septic embolism of interstitial capillaries without focal embolic glomerulonephritis was seen in 1 case each of scarlet fever and diphtheria. Periarteritis nodosa involving most of the abdominal organs and the heart was seen in a woman of 27, who developed hematuria, albuminuria and nitrogen retention 3 weeks after the onset of scarlet fever. She died, muric, 6 weeks after the beginning of the scarlet fever.*



FIG. 2.—Diphtheria. Bland thromboses without necrosis or inflammation in the glomerular tufts (100 X).

CLINICAL LABORATORY DATA. Urinalysis was available in one-third to one-half of the cases. It was absent in most cases with a short stay in the hospital, as, for example, cases of poliomyelitis admitted in a dying state, and in many baby girls. The proportion of severe albuminuria (2+ to 4+) was highest in diphtheria by far, next most frequent in scarlet fever. Most of the severe cases of albuminuria showed moderate numbers of white cells and casts. Red cells were rarely present and then in a relatively small number.

It was thought that the incidence of bacteremia in relation to the extent and severity of renal changes might be of interest; and par-

* Case to be reported by V. B. Dolgopol.

ticularly hemolytic streptococcic septicemia in reference to interstitial nephritis. It is seen that the highest percentage of positive blood cultures occurs in scarlet fever (79%) and in measles (73%). In both of these four-fifths of the positive cultures were of hemolytic streptococci. Other bacteria grown were *Streptococcus viridans*, pneumococcus, meningococcus and diphtheria bacillus.

Discussion. It will be noted that in this series diffuse glomerulonephritis was rare. It was seen only in scarlet fever, and there only in 3.4% of the cases (2 cases). Estimates as to the clinical occurrence of glomerulonephritis following scarlet fever vary widely but it should be pointed out that most deaths following scarlet fever occur before the third week when nephritis is most likely to occur; and that in only a small percentage of cases is acute glomerulonephritis a cause *per se* of death. Cases dying subsequently of the chronic effects of glomerulonephritis would not, of course, be seen in a hospital for acute infectious diseases. In discussing the pathogenesis of acute diffuse glomerulonephritis Bell¹ describes a proliferation of the glomerular capillary endothelium of varying severity occurring in the course of many infectious diseases, notably in subacute bacterial endocarditis and puerperal sepsis. He calls this lesion "subclinical glomerulitis." When the proliferation is of such intensity that the capillary lumens are blocked, clinical acute glomerulonephritis appears, according to Bell. Thus he believes acute glomerulonephritis and subclinical glomerulitis are continuous and essentially a matter of degree. As mentioned before, actual epithelial-endothelial ratios were not determined in our study. The mere impression of an increased number of nuclei in the glomeruli was noted as "increased glomerular cellularity." Thus whether it is even the same process Bell describes we cannot say. However, in a small number of cases of scarlet fever in Bell's series there was no endothelial proliferation, and in our cases "the increased glomerular cellularity" was not more frequent in scarlet fever than in diphtheria. Consequently we cannot make any inferences as to the significance of the increase in glomerular cellularity or its relation, if any, to glomerulonephritis. In 4 cases with "increased glomerular cellularity" in which urinalysis was available 2 showed albumin and 2 were negative.

Tubular degeneration (toxic nephrosis of Fahr⁴) is the most frequent kidney lesion observed in the infectious diseases. The milder variety (albuminous degeneration) was observed with almost equal frequency in scarlet fever, diphtheria and measles. The more severe varieties (hyaline droplet degeneration and necrosis of tubular epithelium) were more frequent in diphtheria and this coincides with the higher incidence of albuminuria in diphtheria. Of course, cases seen at autopsy would be expected to show the most severe generalized septic and toxic changes; clinically, in non-fatal cases, these histologic changes probably occur far less frequently as estimated by albuminuria, cylindruria, and so on.

It should be mentioned that, since septic complications were the usual cause of death in scarlet fever, a pneumonic complication in measles and pertussis, the changes recorded of a toxic nature must to a considerable extent be attributed to the superimposed infection. However, the severity and frequency of the degenerative lesions in diphtheria far exceed those in other conditions and are as striking as the inflammatory lesions in scarlet fever. While the effects in diphtheria were undoubtedly chiefly the result of the toxin of *C. diphtheriae*, almost one-half the cases had a hemolytic streptococcic sepsis and the findings must be interpreted in the light of this also.

The occurrence of casts in the urine or in the tubules in kidney sections is generally associated with albuminuria. Albuminuria is usually taken to indicate leakage of plasma protein through the glomerular tuft. The fact that, histologically, the glomeruli may appear normal in the presence of severe albuminuria cannot, of course, be used as an argument against a functional derangement of the glomeruli. However, the anatomic tubular injury is so prominent in diphtheria and the parallelism of tubular injury, casts in tubules, and albuminuria so evident in this series as to suggest a significant relationship between the tubular degeneration and the casts. We have, therefore, listed "casts in tubules" as a tubular lesion. This is also convenient for the mere fact that casts are actually seen in the tubules whatever the nature of their origin.

Interstitial nephritis was observed most commonly in scarlet fever and no other condition approached it in the severity of these changes. The percentage of hemolytic streptococcus sepsis was approximately the same in measles as in scarlet fever but interstitial nephritis was much less common in measles and of a milder degree. In diphtheria, although the incidence of streptococcic sepsis and interstitial nephritis was parallel, the changes again were of a much milder degree. Thus, while the argument for the relationship of streptococcic sepsis, in general, and interstitial nephritis is strong, there would appear to be a particularly violent and frequent reaction in scarlet fever. Kimmelstiel¹ states that this lesion is usually found at autopsy without any history of a disturbance of renal function. He describes 6 cases of anuria with azotemia in infections, burns and other diseases which showed interstitial nephritis at autopsy. However, he concludes that the anuria was not proved to be of renal origin and, in any event, may be merely coincident with the anatomic renal lesion and have no causal relationship. He found the lesion present in various types of hemolytic reactions, especially following blood transfusions, and in liver disease or injury—the so-called hepatorenal syndrome. He regards the lesion as an anaphylactoid or hyperergic response to foreign protein or protein split-products, and not specifically a reaction to streptococcic toxins, as do Brody and Smith.²

No attempt at clinico-pathologic correlation in cases of interstitial nephritis was made here beyond comparison of the presence and

severity of albuminuria and of the histologic lesion. No parallelism was found. The severest grades of interstitial nephritis were often accompanied by little or no albuminuria, and many 3+ and 4+ albuminurias occurred in the absence of the lesion.

The bland thromboses of individual glomerular loops without necrosis or inflammation found in a few cases were of uncertain significance or duration. It was felt that they might represent a terminal process associated with stagnation of blood. The otherwise normal appearance of the thrombosed loop argued against an embolic or a septic thrombotic process, either one of which may be the mode of origin of actual focal embolic glomerulonephritis. The latter lesion was seen in a few cases in this series and was very different.

The embolic interstitial lesion seen, septic and aseptic, differed in no way from those not associated with an infectious disease.

The occurrence of periarteritis nodosa after scarlet fever is mentioned by Friedberg and Gross.⁴

Rather conspicuous by its absence in this series is suppurative pyelonephritis. Despite the presence of moderate numbers of white cells, along with albumin and casts in the urine, in many cases, especially of diphtheria, no suppurative lesion was found in the kidneys. It should be recognized that these urinary findings in the acute infectious diseases may be the result of toxic injury to the kidney and do not necessarily indicate suppuration of the urinary excretory tract.

Summary. Acute diffuse glomerulonephritis is rare in cases of the common acute infectious diseases coming to autopsy. It was present only in 3.4% of scarlet fever and in no other disease.

Tubular degeneration is the most frequent lesion in the kidney in all the acute infectious diseases. The more severe degenerative changes are most frequent in diphtheria. Hyaline droplet degeneration was present in 25%, epithelial necrosis in 16% of cases of diphtheria.

Interstitial nephritis occurs most often in scarlet fever (77%). Interstitial nephritis and streptococcic hemolytic sepsis are parallel in scarlet fever and diphtheria but not in measles where streptococcic sepsis is three times as frequent as the nephritis.

Pyelonephritis was not found in this series.

Albuminuria was very frequent in all diseases.

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ACUTE PORPHYRIA.*

BY SAMUEL NESBITT, M.D., PH.D. (IN MED.),
INSTRUCTOR IN MEDICINE, YALE UNIVERSITY SCHOOL OF MEDICINE, NEW HAVEN,
CONNECTICUT,

AND

CHARLES H. WATKINS, M.D., PH.D.,
DIVISION OF MEDICINE, MAYO CLINIC,
ROCHESTER, MINN.

THE porphyrias may be classified as congenital and acute porphyrias, and the acute porphyrias may be classified further as acute toxic porphyria and acute idiopathic porphyria.^{4b,9,12} Excellent reviews of the subject have appeared during recent years^{3,9,16a,b,17,18} and it would seem that the number of patients who have acute porphyria is increasing comparatively rapidly. This may well be accounted for by the fact that physicians are becoming better acquainted with this disease and are more on the alert to recognize a case when it is presented to them. Up to 1939 fewer than 30 cases of congenital porphyria had appeared in the literature, about 100 cases of acute toxic porphyria and 153 cases of acute idiopathic porphyria.^{3,16} Several additional cases of acute porphyria have been published recently^{5,7,8,10,15} but the number of cases of congenital porphyria in the literature has not been augmented.

It has been pointed out frequently^{9,18} that the acute toxic forms and the acute idiopathic forms of porphyria are indistinguishable, either clinically or by laboratory methods. The acute toxic form of porphyria is recognized only on the basis of the presence of a toxic agent which apparently is an etiologic factor. Eldahl^{4a} claimed that there are other precipitating factors such as anxiety, exhaustion and infection.

Acute porphyria^{9,18} of either type is characterized by gastrointestinal disturbances and involvement of the central nervous system. There may or may not be fever. Commonly there is severe abdominal pain which may be generalized or which may be confined to the lower part of the abdomen. There may be nausea, vomiting, constipation and ileus; in addition there may be mild jaundice. There is occasionally a diffuse or spotted pigmentation of the skin, but not of the mucosa, the nature of which is unknown. Involvement of the central nervous system is exhibited most frequently by an ascending (Landry) type of paralysis, and death is frequently due to bulbar involvement with respiratory failure. There are frequently delirium and hallucinations. Photosensitivity occurs rarely in acute porphyria. Pathologic changes in the central nervous system at necropsy have been reviewed extensively.⁹

* Abridged portion of thesis submitted by Dr. Nesbitt to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D. in Medicine.

Schulte studied patients who had acute toxic porphyria and expressed the belief that the disease is due to the action of the toxic agent. His work and the work of others convinced Mason and associates that the toxic agent, usually a barbiturate, in some manner produces the disease and that a constitutional liability need not necessarily be assumed in every instance, it being reasonable to assume that acute toxic and acute idiopathic porphyrias are caused by some endogenous or exogenous intoxication which affects certain persons who may have an idiosyncrasy to certain drugs. It might be assumed, of course, that there is always some toxic agent involved as an etiologic factor but that in cases of acute idiopathic porphyria the toxic agent remains unrecognized. Support for such an assumption might be interpreted from a report by Weiss²⁰ of 2 patients in whom acute idiopathic porphyria developed, 1 of the patients having replaced the initial patient in the capacity of cook in a particular restaurant.

Günther,⁶ who first described the porphyrias, expressed the opinion that the disease in all instances represents a constitutional anomaly of pigment metabolism. Subsequent work, especially those case reports which indicate that the porphyrias are a familial disease, has done much to confirm Günther's original idea. Families have been observed in which more than one member was afflicted with the manifestations which are considered to be characteristic of acute porphyria; in a few instances one member of the family suffered from acute porphyria while another member of the same family suffered from congenital porphyria.¹⁸ Barker and Estes² early reported a very remarkable instance in which two sisters died of acute idiopathic porphyria while a third sister, the mother and maternal grandmother presented histories of abdominal colic, accompanied by constipation, vomiting and the voiding of very dark urine. Waldenström^{16a} described many such families in which often both the acute toxic and the acute idiopathic forms may occur in the same family, and he claimed that the disease is inherited and transmitted as a dominant Mendelian characteristic. Turner demonstrated that the error in metabolism is not limited to the periods of acute symptoms in these patients, but that they may excrete uroporphyrin and its metal complex between such episodes. In acute toxic porphyria a definite precipitating factor is apparent to explain the acute episodes, but the cause of such episodes in acute idiopathic porphyria remains obscure.

The diagnosis of acute porphyria of either type depends on an evaluation of the clinical picture and must be confirmed by an examination of the urine. At one time it was believed that the demonstration of uroporphyrin in the urine of such patients was necessary to establish the diagnosis,^{16a} but several cases of porphyria have been reported in which uroporphyrin was not excreted in the urine^{1,11,12} but other characteristic pigments were present. Usually

patients who have acute porphyria excrete uroporphyrins III and I in the urine with a great predominance of the Type III isomer. Uroporphyrin has not been demonstrated in the feces of such patients, which usually contain only a small amount of coproporphyrin III. It has been shown recently that uroporphyrin may be excreted as a metal complex^{3,11} and between the acute episodes the fraction of uroporphyrin which is present as a metal complex may be increased. Usually only a relatively small amount of coproporphyrin III is present in the urine.¹⁴ Waldenström,¹⁵ and Waldenström and Vahlquist described in the urine of such patients the presence of a "porphobilinogen" which on standing or on adding acid and boiling is converted into uroporphyrin III and a very little amount of uroporphyrin I. It is becoming more and more evident that other pigments are involved in this metabolic disorder. Pigments other than porphyrins may account for most or all of the dark color of the urine of these patients. Turner expressed the opinion that urofuscin accounted for most of the color in the urine of such a patient which he investigated. Waldenström and Vahlquist expressed the belief that pigments made up of several united pyrrol nuclei may be present in such urine while other workers claim that urofuscin, skatol red or urobilin may constitute most of the color of the urine.

Case Reports. **CASE 1.**—The patient, a 34-year-old American-born man, employed as a clerk, always had enjoyed excellent health and never had observed anything unusual about the color of his urine. Seven months before coming to the Mayo Clinic he had had a carious impacted third molar tooth removed. An infection occurred in the tooth socket which was sufficiently severe to warrant hospitalization and he was given sulfanilamide. During the first 36 hours 100 gr. (6.5 gm.) of sulfanilamide was administered, but then the drug was discontinued because of the onset of severe, generalized abdominal pain, cramps and ileus, and it was observed that the patient's urine was the color of grape juice although it did not contain blood. The abdominal pain and red urine persisted and 10 days later the onset of generalized paresthesia, consisting of a burning, scalding sensation, was noted over the face and body. Six weeks later the patient's gait became shuffling until he could not walk because of the gradual onset of paralysis of his legs and then of his arms. He became incontinent of urine and feces and an indwelling catheter was used. During this time he acquired a chronic urinary infection. For 6 or 8 weeks he experienced transient episodes of delirium and hallucinations and during much of this time he had to be fed through a tube. Three months before coming to the clinic he first noted some return of function in that he could move his toes, and within 2 months he could shuffle along unaided. Gradually his sphincteral control of urine and feces returned. Frequently throughout this period his urine would be dark red for several days at a time. He had lost 50 pounds (22.7 kg.) during the illness.

The patient's family history was interesting in that his mother had died during an illness similar to that of the patient. She had suffered from severe abdominal cramps and paralysis and had voided very dark red urine.

Physical examination revealed an emaciated, gaunt young man who had great difficulty in progressing by means of a shuffling gait. The blood pressure was 120 mm. of mercury systolic and 80 diastolic. The pulse

rate was 104 and the temperature by mouth 98.6° F. There were marked and symmetrical weakness of the lower extremities which was graded -3 to -4 (on the basis of 1 to 4) and symmetrical weakness of the shoulder girdle and upper extremities which was graded -2 to -3. There were also marked atrophy and loss of muscle tone over these distributions. The biceps, triceps and patellar reflexes were absent bilaterally. The Achilles reflexes were present and about equal. No Babinski or Hoffman reflex was present. There were no sensory changes apart from hyperesthesia which was present over both the upper and lower extremities. It was noted that the paralysis was more nearly a radicular type than a peripheral paralysis and that from the history of delirium and of loss of sphincteral control there must have been involvement of the cerebrum and spinal cord.

Laboratory Studies. The concentration of hemoglobin was 14 gm. per 100 cc. of blood; the erythrocytes numbered 5,200,000 and the leukocytes 7500 per c.mm. of blood. The percentages of the various types of leukocytes were as follows: lymphocytes 30.4, monocytes 1.5, neutrophils 65, eosinophils 2, and basophils 1. There were hyaline casts grade 2 in the urine and pyuria was graded 2 (on a basis of 1 to 4 in which 1 indicates the least and 4 the greatest concentration). Culture revealed *Escherichia coli*. Excretion of sulphonephthalein was 25%. The flocculation reaction for syphilis was negative. The concentration of urea was 48 mg. per 100 cc. of blood, the concentration of bilirubin was 1 mg. per 100 cc. of serum with an indirect van den Bergh reaction and the sedimentation rate was 8 mm. per hour. Liver function test (bromsulphalein) did not show dye retention. Roentgenographic examination of the chest gave negative results.

The amount of coproporphyrin excreted in the urine of this patient was determined each day both in the fresh specimen and in the urine after it had remained exposed to the air and sunlight for several hours. The fresh urine was brownish red but became a little darker on standing. These results are represented in Table 1. From the pooled urine collections 0.64 mg. of uroporphyrin III was isolated and identified, the melting point of the methyl ester being 260° C. An amount of uroporphyrin I (too small to weigh) was isolated, the melting point of its methyl ester being 301° C.

TABLE 1.—EXCRETION OF ETHER-SOLUBLE PORPHYRIN IN THE URINE (CASE 1).

Day.	Volume of urine, cc.	Coproporphyrin, micrograms per 100 cc. in 24-hr. specimen.		Nicotinic acid, mg. per day.
		Fresh urine.	After standing.	
1	1425	952	1454	0
2	1065	614	964	0
3	685	345	543	0
4	1095	552	867	0
5	1205	716	1125	100
6	660	196	307	150
7	680	428	672	300
8	1095	283	445	300
10 months later	1800	0	299	0

A small amount (too little to weigh) of coproporphyrin III was isolated, the melting point of its methyl ester being 143° C.; no coproporphyrin I was isolated from the urine. It was demonstrated that the zinc metal complex of uroporphyrin was present in this urine. The native urine exhibited the two typical absorption bands of the metal complex at 577 and 541 millimicrons. On the addition of a few drops of concentrated hydrochloric acid to the urine in the cuvette these bands promptly disappeared and were replaced by the bands of uroporphyrin. On long standing, deep brown crystals in beautiful rosettes separated from the urine from which porphyrins had been removed. These crystals did not melt up to

300° C. and they were insoluble in the usual organic solvents, including ether, acetone, chloroform, carbon tetrachloride, methyl alcohol, amyl alcohol and 25% hydrochloric acid. The nature of this substance is as yet to be determined.

CASE 2.*—The patient, a 33-year-old housewife, had been underweight and chronically fatigued. There was nothing to suggest porphyria in other members of the family. During the past 3 years she had experienced 9 episodes characterized by cramping pains in the right lower part of the abdomen and in the midabdomen, often so severe that morphine did not relieve them. There was usually some epigastric distress, nausea and vomiting with these attacks, which lasted from a few days to several weeks. During these episodes the patient usually became depressed mentally, expressed a feeling of impending death, and would become so irrational as to suggest the possibility of encephalitis. On several of these occasions it was observed that her urine was strikingly dark and red like port wine.

One month after the most recent episode, at the patient's urgent request, operation was performed. At this time the physical examination gave essentially negative results. The urine was straw-colored and did not show any abnormalities with the usual tests. The erythrocytes numbered 4,050,000 per c.mm. of blood and the leukocytes 8200. The concentration of hemoglobin was 12 gm. per 100 cc. of blood. The percentages of the various types of leukocytes were as follows: neutrophils 60, lymphocytes 36, mononuclears 2 and eosinophils 2. Operation consisted of removal of a right ovarian cyst the size of an olive, appendectomy and uterine suspension.

Four days after operation the patient began to menstruate and complained of severe pains in the lower part of her abdomen which did not abate in severity following cessation of the menstrual flow. Her temperature rose to 102° F. The abdominal pains became more severe and the patient became apathetic and felt that she was going to die; it was observed that her urine had become dark red. She became increasingly confused mentally and complained of a tight, choking sensation in her throat. She also complained that her tongue felt thick and her speech was not clear. She experienced respiratory distress and an inability to get air into the lungs although there was no evidence of pulmonary edema. Her respirations became labored and shallow and she expired on the seventeenth postoperative day, apparently from bulbar paralysis, despite supportive measures which included the use of oxygen.

A 400-cc. specimen of this patient's urine† was received for examination. The urine was very dark red brown. It was found to contain 1.057 micrograms of ether-soluble porphyrin per cc. of urine. It was further demonstrated by means of the method which has been described recently by Watson¹⁹ that coproporphyrin III comprised 88% of this porphyrin, the remainder being coproporphyrin I. From this single specimen of urine 0.621 mg. of uroporphyrin III was isolated as the methyl ester, melting point 270° C. A small amount (too little to weigh) of uroporphyrin I was isolated, the melting point of the methyl ester being 301° C. Spectroscopic examination of the native urine revealed that the uroporphyrin was present as the zinc metal complex.

CASE 3.—The patient, a 51-year-old American-born housewife, complained of repeated attacks of dysphagia, abdominal bloating and profound weakness, during which periods her urine had been observed to be extremely

* Dr. C. J. Watson, of the University of Minnesota, also has investigated this case including a study of feces and urine as well as blood, kidneys and liver obtained at necropsy.

† We are indebted to Dr. C. E. Lynn of Dubuque, Iowa, for having furnished us the account of this patient's illness as well as having furnished us with the urine specimen for examination.

dark red. The family history was not remarkable and the patient's past history presented only the story of a chronic duodenal ulcer. Two years previously on two occasions she had observed that her urine suddenly became very dark red and stayed so for approximately 10 days, during which time she complained only of some fatigue and weakness and noticed that her skin appeared to become a little yellow. During the year before coming to the clinic she had experienced approximately 8 episodes lasting from 2 or 3 days to several weeks which were initiated and characterized throughout by the very dark red color of her urine. During these periods she complained principally of dysphagia, and that cold and solid foods seemed to stick beneath the sternum before entering the stomach. She also experienced profound weakness, abdominal bloating, and dyspnea on exertion, and her skin appeared to become somewhat yellow. At such times she always had been found to be anemic, and on several occasions had required repeated blood transfusions. During several of these attacks she had exhibited psychotic manifestations which suggested a paranoid trend.

On examination she was somewhat undernourished and pale and there was questionable jaundice. Otherwise there were no findings of note. Special examination of the central nervous system was carried out but with negative results.

Laboratory Studies. The concentration of hemoglobin was 10.1 gm. per 100 cc. of blood; the erythrocytes numbered 2,970,000 per c.mm. of blood and the leukocytes 10,500. A blood smear revealed a macrocytic type of anemia. The routine flocculation tests for syphilis gave negative results. The urine was acid in reaction and its specific gravity was 1.019. Albuminuria was graded +3 (sulphosalicylic method). Pyuria and erythrocyturia were each graded 1 (on a basis of 1 to 4) and granular casts were graded 4. The basal metabolic rate was +2%. The percentages of the various types of leukocytes were as follows: lymphocytes 39.5, monocytes 3.5, neutrophilic leukocytes 56, eosinophils 0.5, and basophils 0.5. There were 256,000 platelets per c.mm. of blood. The Donath-Landsteiner reaction for autohemolysins was negative. Erythrocyte fragility was within the normal range and the time for clot retraction was normal. The concentration of urea ranged from 20 to 82 mg. per 100 cc. of blood, the concentration of creatine was 1.5 mg. per 100 cc. of blood and the concentration of sulphates was 8.8 mg. per 100 cc. of serum. The concentration of bilirubin was 1.8 mg. per 100 cc. of serum and the van den Bergh reaction was indirect. The concentration of proteins was 6.3 gm. per 100 cc. of serum with an albumin-globulin ratio of 3.5/1. A fasting concentration of sugar was 94 mg. per 100 cc. of blood. A catheterized specimen of urine showed no growth of organisms. Repeated spectroscopic examination of the urine revealed the presence of porphyrin which was not identified further and also of oxyhemoglobin. Roentgenographic examinations of the chest, esophagus, colon and terminal portion of the ileum gave negative results. Evidence of a duodenal ulcer was visualized.

While in the hospital under observation the patient exhibited several episodes as previously described during which times her urine, otherwise normal in appearance, became very dark brown or reddish-brown. It was believed that she had paroxysmal hemoglobinuria with nephritis and renal insufficiency. Considerable thought had been given to the possibility of porphyria. On her return to her home her condition remained much the same, the attacks becoming more frequent and more severe. Treatment consisted of Roentgen and radium therapy over the splenic area and moccasin venom, as well as iron by mouth and injection of liver extract.

Eighteen months after her first visit the patient again returned to the clinic where she remained under observation for a period of 1 month. She continued to have attacks just as before, although she now complained of considerable pain in the epigastrium and left upper quadrant during the

attacks. During the times between these episodes she felt perfectly well except for some weakness after each attack. The results of physical examination and laboratory findings were essentially the same as at the time of her initial visit. Cold tests by means of immersing the patient's limbs in cold water at 10° to 12° C. for a period of 1 hour failed to precipitate an attack or to produce hemolysis. The amount of ether-soluble porphyrin excreted daily in the urine and feces was within normal limits, ranging from 19 to 41 micrograms and 193 to 458 micrograms respectively. Spectroscopic examination of the blood showed the absorption bands which are characteristic of oxyhemoglobin. The concentration of bilirubin ranged from 1.6 to 2.4 mg. per 100 cc. of serum with an indirect reaction. A liver function test (bromsulphalein) showed no dye retention. The concentration of protein was 7.5 gm. per 100 cc. of serum with an albumin-globulin ratio of 1.1/1.

After leaving the clinic the patient's condition remained much the same, being characterized by frequent episodes of dysphagia, weakness, dyspnea, severe abdominal pains and mental depression, and during such times her urine was extremely dark red or brown. She expired 5 years after her first visit to the clinic and her local physician has given us an account of the terminal event and submitted necropsy material for our examination. The patient had cystitis and complained of constant nausea and vomiting and distress in the lower part of the abdomen. She was deeply jaundiced and the stools were clay-colored. The liver was palpable and there was considerable tenderness in the right upper quadrant of the abdomen. There was severe achromic anemia, the hemoglobin being 35%. She died rather suddenly, apparently from what was believed to be an acute cardiorespiratory collapse. The impression was that the patient had died of acute hepatic degeneration of unknown cause.

*Necropsy.** The lungs were described as being bronzed in appearance. The serum draining from clotted blood contained within the heart was of a bright, clear cherry color. The liver showed mild passive congestion; obstruction of the continuity of the bile passages could not be demonstrated. The spleen was increased in size and was rather firm. The kidneys showed evidence of considerable chronic damage and the entire kidney substance was of a deep bronze color.

Sections were prepared at the clinic for histologic examination† which included liver, spleen, bone marrow and kidney. There was much central necrosis of the liver cells. In some regions the necrosis was accompanied by an increase in the number of neutrophils. Many of the liver cells contained an increased amount of brownish-yellow pigment. In the spleen there was active proliferation of reticular cells with occasional mitotic figures and large multinucleated cells. There was hyaline fibrinoid change in the reticular cells of some of the Malpighian bodies. The bone marrow appeared hyperplastic but it was difficult to determine which cells were involved in the hyperplasia. Normoblasts were numerous. There was pyelonephritis with beginning abscess formation. Unusual findings were peculiar red casts which filled many of the renal tubules and the large amount of iron which was present in the epithelial cells.

CASE 4.—The patient, a 20-year-old single, American-born woman, had enjoyed good health until 3 years before coming to the clinic when she had noticed some pruritus of the exposed portions of the body, including the face and hands, followed by a mild vesicular eruption. She continued to have this sort of difficulty periodically and had noticed that the onset of the dermatitis seemed to be related to exposure to sunlight. These attacks

* We are indebted to Drs. W. H. Barrow and H. A. Ball, San Diego, Calif., who furnished the clinical account of the patient's terminal illness and a description of the necropsy which was performed, as well as the tissues which we examined.

† We are indebted to Dr. A. H. Baggenstoss for this histologic study.

increased in severity and on several occasions she had had severe bullous lesions over her face, hands and ankles. Seven months before coming to the clinic the patient had complained of severe abdominal pain, nausea and vomiting and at that time her appendix had been removed. During that period it is to be noted that she exhibited mild psychotic behavior. The abdominal pain returned soon after operation and persisted until she came to the clinic. This pain was so severe that it doubled her up, was of a cramp-like nature and was rather diffuse about the region of the umbilicus.

Physical examination revealed much scarring with some pigmentation of the face, wrists and ankles, where the patient formerly had had her skin eruption. There was rather diffuse tenderness of the abdomen with no localizing features.

The urine was observed to be reddish-brown and contained some granular casts and a few pus cells. The concentration of hemoglobin was 14.2 gm. per 100 cc. of blood; the erythrocytes numbered 4,710,000 and leukocytes 8500 in each c.mm. of blood. The percentages of the various types of leukocytes were as follows: lymphocytes 32.5, monocytes 6.5, neutrophils 56.5, eosinophils 3.5, and basophils 1. Examination of the blood smear showed nothing of significance. Routine flocculation tests for syphilis gave negative results. The erythrocyte sedimentation rate was 43 mm. per hour. Culture of the urine showed no growth. The concentration of urea was 54 mg. per 100 cc. of blood and the concentration of chlorides was 476 mg. per 100 cc. of plasma. The concentration of bilirubin was 1.8 mg. per 100 cc. of serum on admission and the van den Bergh reaction was direct. The concentration of proteins was 8 gm. per 100 cc. of serum with an albumin-globulin ratio of 1.1/1. Roentgenographic examination of the chest gave negative results and a simple roentgenogram of the abdomen was negative. The urine was demonstrated to contain large amounts of coproporphyrin and uroporphyrin and it was demonstrated spectroscopically that the uroporphyrin was present as the zinc metal complex. The blood serum contained sufficient porphyrin to fluoresce in ultraviolet light; at least some of the porphyrin was ether-soluble. Light tests for photosensitivity were carried out and it was found that the patient was sensitive to the far ultraviolet part of the spectrum but, more particularly, to the red portion of the spectrum, which produced large urticarial lesions with severe pruritus.

The patient continued to complain of severe abdominal pain. She could not retain anything by mouth and vomited continually. The concentration of bilirubin became elevated to 19.8 mg. per 100 cc. of serum and the van den Bergh reaction was direct. The Quick prothrombin time became elevated from 23 seconds (normal, 20 seconds) to as high as 29 seconds.

Treatment consisted of the intravenous administration of 5% glucose in physiologic saline solution to which was added thiamin chloride and nicotinic acid. Liver extract was also administered intramuscularly. A feeding formula was employed; the food was administered by duodenal tube. The patient gradually improved. However, at the time of her dismissal the concentration of bilirubin was 17.6 mg. per 100 cc. of serum and the van den Bergh reaction was direct. Since she left the hospital her jaundice has cleared and she has complained only of considerable pruritus of the face. A detailed account of this case is to be published, including laboratory findings and tests for photosensitivity.

Comment. Three cases of acute porphyria (Cases 1, 2 and 4) have been described in which the diagnosis was confirmed by the demonstration of large quantities of uroporphyrin in the urine, most of which was of isomeric series III, there being a small fraction only of uroporphyrin I. It was shown by spectroscopic examination that this occurred as the zinc metal complex. Another case has

been described (Case 3) which presented the usual clinical picture of acute porphyria but which was diagnosed as paroxysmal hemoglobinuria on the basis of spectroscopic studies which demonstrated the presence of oxyhemoglobin in both the urine and blood serum during crises. It is suggested that this case actually represents a case of acute porphyria, and that the absorption bands which were observed and believed to be those of oxyhemoglobin were probably those bands of the zinc metal complex of uroporphyrin. The error might be explained easily since oxyhemoglobin produces absorption bands at 585 to 567 millimicrons and 550.7 to 527 millimicrons with maximal absorption which corresponds almost precisely with the bands of uroporphyrin zinc metal complex at 577 and 541 millimicrons respectively. The bands of the uroporphyrin zinc metal complex are distinguished only by the fact that, when a little concentrated hydrochloric acid is added, the metal complex is broken up and the bands are replaced immediately by the bands of uroporphyrin. Unfortunately no urine was procurable from this patient at the time of the present investigation which would have made it possible to make the differentiation one way or the other.

Case 1 is interesting because of the family history which would indicate that acute porphyria is just as much a familial disease as is congenital porphyria and that the underlying mechanism is an inborn error of metabolism, as originally suggested by Günther. This patient had taken sulfanilamide just antecedent to his illness, and it is possible that this may have acted as a precipitating toxic factor. His urine was shown to contain the zinc metal complex of uroporphyrin as well as unusually large quantities of coproporphyrin nearly a year after his acute illness and when he had shown considerable improvement. While under observation it could not be demonstrated that fairly large doses of nicotinic acid by mouth produced any effect upon the degree of porphyrin excretion.

Case 2 presents a picture of the usual course of porphyria. There was no family history to suggest porphyria in other members of this patient's family and no toxic agent could be shown to be a possible precipitating factor. Patients who have acute idiopathic porphyria and patients who have acute toxic porphyria present the same clinical picture and the same laboratory findings and probably represent the same disease, the only difference being that in one instance it happens to be possible to point out a substance which may have been a precipitating factor.

The description of Case 3 includes an interesting histologic study of tissues which were obtained at necropsy.

The fourth case represents the rather unusual condition of photosensitivity in the acute form of porphyria.

These 4 cases of acute porphyria were observed during the past 3 years. It would seem that the disease is not as unusual as has formerly been supposed and that with a more general knowledge of the subject more cases will be detected.

Summary and Conclusions. Acute idiopathic porphyria and acute toxic porphyria probably represent the same condition and both should simply be included under the term acute porphyria which is a disease caused by an inborn error of porphyrin metabolism.

The disease manifests itself clinically by any one or a combination of events which include a familial history; various types of gastrointestinal disturbances and abdominal pain; red or dark reddish brown urine; involvement of the central nervous system, as evidenced by psychotic manifestations or paralysis, usually of the ascending type; jaundice; renal damage; and rarely pigmentation of the skin or dermal photosensitivity.

A discussion of the chemical aspects of the problem has been included and it is pointed out in what manner oxyhemoglobin and the zinc metal complex of uroporphyrin may be differentiated by spectroscopic means.

Case reports are presented of 4 patients who had acute porphyria and who have been encountered during the past 3 years and it is suggested that this disease entity is not so rare as hitherto has been supposed.

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PHOSPHORUS METABOLISM OF BLOOD OF PATIENTS WITH LEUKEMIA AND POLYCYTHEMIA.*

By L. A. ERF, M.D.,

WILLIAM R. KENAN, JR., FELLOW,

AND

L. W. TUTTLE,

BERKELEY, CALIF.

(From the Crocker Radiation Laboratory and Department of Medicine, University of California.)

In a previous paper⁵ the distribution of radio-phosphorus (P^{32}) following its oral administration was noted in the blood of 2 patients with myeloid leukemia; and a suggestion was made that the rapid

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uptake of phosphorus by the white blood cells during the hours immediately following the administration was probably concerned with the carbohydrate metabolism of the cells, while that retained days after administration was probably associated with the nucleoprotein metabolism of the cells. This paper presents the amount of radio-phosphorus retained at various intervals of time in the "phospholipid," "acid-soluble," and "nucleoprotein" fractions of circulating red blood cells, white blood cells and plasma of patients with leukemia and polycythemia who received either orally or intravenously "therapeutic," and not "tracer," doses of radio-phosphorus.³

Materials and Methods. All of the patients had been diagnosed and treated elsewhere by means other than radio-phosphorus many months before admission. The radio-phosphorus was produced by the Berkeley cyclotron.² The separation⁴ and fractionation⁴ of tissues and cells have been described previously. The techniques might be summarized as follows: Cooled heparinized venous blood (the amount varying from 20 to 50 cc.) was centrifuged, the blood elements separated and each recentrifuged in heparinized buffer solution exactly 20 minutes at 1450 times gravity to insure constant volumes; and the "phospholipid" fractions were extracted by use of alcohol, ether and reflux condensers, the "acid-soluble" by ice cold 5% trichloroacetic acid, while the residue was considered the "nucleoprotein" fraction. The radioactivity assays were determined by means of a DuBridge electrometer. The total phosphorus (P^{31}) content of the various fractions was determined by the method of Pregl.⁵

Results. The results are tabulated on the two accompanying tables. In Table 1 are listed the amounts of radio-phosphorus (P^{32}), as microcuries per cubic centimeter, or percentage of the dose administered per 100 cc. of packed red blood cells or packed white blood cells or plasma, retained in the various fractions 4 to 96 hours (21 days in one instance) after the administration of "therapeutic" doses of radio-phosphorus to 1 patient with lymphoid leukemia, 1 with myeloid leukemia and 2 with polycythemia. As can be observed, the greatest quantities of P^{32} were retained in the "acid-soluble" fraction of the red blood cells, white blood cells and plasma of all of the patients. However, the quantities in this fraction apparently reached a peak between the 12th and 24th hours after administration and then decreased, as did those of the "phospholipid" and "nucleoprotein" fractions of the red blood cells, but the quantities in the latter 2 fractions of the white blood cells and plasma gradually increased to the 96th hour, as can be observed. In 1 patient (Wer) equal amounts of radio-phosphorus were administered orally and intravenously and as is illustrated, much greater quantities were retained in all the fractions when P^{32} was given by the latter route.

In Table 2 are listed the average total phosphorus (P^{31}) content of the fractions of red blood cells, white blood cells and plasma of the 2 patients with leukemia. One finding of significance is that

TABLE 1.—RETENTION OF RADIO-PHOSPHORUS IN VARIOUS FRACTIONS OF THE CIRCULATING BLOOD OF PATIENTS WITH LEUKEMIA AND POLYCYTHEMIA.*

Name of patient and wt. in lbs.	Type of disease.	Amt. of P ₃₂ adm. in μ c.†	Route of adm.†	Amt. of sodium phosphate in which P ₃₂ was incorp. (g.).	Hours after adm.	Red blood cells.						White blood cells.						Plasma.					
						Phospholipid.		Acid soluble.		Nucleo-protein.		Phospholipid.		Acid soluble.		Nucleo-protein.		Phospholipid.		Acid soluble.		Nucleo-protein.	
						μ c/cc.† dose/100 cc.	μ c/cc.	% of dose/100 cc.	μ c/cc.	% of dose/100 cc.	μ c/cc.	% of dose/100 cc.	μ c/cc.	% of dose/100 cc.	μ c/cc.	% of dose/100 cc.	μ c/cc.	% of dose/100 cc.	μ c/cc.	% of dose/100 cc.	μ c/cc.	% of dose/100 cc.	μ c/cc.
Ab 135	Lymphoid leukemia	5000	O	.75	12 24 48 96	.0002 .0006 .0008 .0007	.0005 .0111 .0395 .0013	.0433 .0870 .1180 .0790	.0300 .0147 .0162 .0320	.0047 .0095 .0192 .0310	.0441 .0413 .0385 .0373	.0880 .0820 .0800 .0745	.0160 .0078 .0107 .0210	.0007 .0010 .0013 .0027	.0069 .0053 .0050 .0037	.0140 .0110 .0100 .0070	.0003 .0003 ..	.0013 .0027 .0023 .0010	.0069 .0053 .0050 .0037	.0140 .0110 .0100 .0070	.0003 .0003 ..		
Kli 246	Myeloid leukemia	1950	I.V.	.30	4 24 48 96	.0011 .0014 .0015 .0011	.0066 .0075 .0043 .0066	.0114 .0121 .0078 .0057	.0630 .1140 .0460 .0330	.0123 .0085 .0054 .0029	.0029 .0064 .0061 .0093	.0320 .0312 .0263 .0192	.1700 .1680 .1500 .1080	.0044 .0095 .0121 .0172	.0013 .0031 .0055 .0070	.0079 .0051 .0038 .0032	.0131 .0083 .0063 .0053	.0008 .0020 .0015 .0029	.0013 .0021 .0031 .0038	.0079 .0051 .0038 .0032	.0131 .0083 .0063 .0053	.0008 .0020 .0015 .0029	
Wil 105	Polycthemia	6000	I.V.	.42	12 24 48 96	.0007 .0008 .0015 .0032	.0011 .0013 .0025 .0053	.0868 .0660 .0630 .0336	.1420 .1090 .1040 .0557	.0095 .0510 .0324 .0226	.0072 .0156 .0153 .0063	.0119 .0258 .0253 .0104	.1160 .1260 .1400 .0748	.0108 .0163 .0358 .0315	.0013 .0031 .0055 .0070	.0079 .0051 .0038 .0032	.0131 .0083 .0063 .0053	.0008 .0020 .0015 .0029	.0013 .0021 .0031 .0038	.0079 .0051 .0038 .0032	.0131 .0083 .0063 .0053	.0008 .0020 .0015 .0029	
Wer 184	Polycthemia	2550	O	.178	24 48 96 21 da.	.0005 .0008 .0009 .0014	.0019 .0031 .0035 .0055	.0260 .0230 .0211 .0032	.1020 .0900 .0825 .0126	.0016 .0086 .0067 .0008	.0027 .0051 .0120 .0050	.0106 .0200 .0470 .0196	.0720 .0925 .0875 .0235	.0031 .0171 .0177 .0055	.0013 .0022 .0029 .0018	.0051 .0086 .0114 .0070	.0022 .0153 .0022 .0004	.0086 .0039 .0022 .0004	.0106 .0117 .0086 .0001	.0003 .0019 .0007 .0001	.0003 .0019 .0007 .0001		
		2550	I.V.	.167	24 48 96	.0029 .0034 .0030	.0114 .0133 .0118	.0490 .0338 .0208	.1320 .1320 .0815	.0011 .0088 .0062	.0142 .0271 .0452	.0556 .1070 .1750	.0965 .0750 .2070	.0078 .0226 .0293	.0034 .0110 .0052	.0133 .0431 .0204	.0106 .0086 .0019	.0005 .0005 .0006	.0005 .0005 .0006	.0019 .0019 .0023	.0005 .0005 .0006		

* All calculations corrected for weight of patients (to 150 pounds) and for decay of P₃₂ to date of administration.
† μ c. = microcuries.
‡ O = oral; I.V. = intravenous.

there is much more phosphorus in the nueleoprotein fraction of lymphoid than myeloid leukemic cells. This is probably due to the relatively greater volumes of the nuelei of these particular lymphoid cells.¹ Another finding is, that there is very little phosphorus present in the "nueleoprotein" fraction of plasma.

TABLE 2.—AVERAGE (FOUR DETERMINATIONS FOR EACH FIGURE REPRESENTED) TOTAL PHOSPHORUS (MG. OF P^{31} PER CC.) CONTENT OF THE FRACTIONS OF THE BLOOD OF 2 PATIENTS WITH LEUKEMIA.

	Ab (lymphoid leukemia).	Kli (myeloid leukemia).
Red blood cells:		
Phospholipid71	.11
Acid soluble51	.37
Nucleoprotein25	.11
White blood cells:		
Phospholipid52	.43
Acid soluble94	.56
Nucleoprotein	3.04	.89
Plasma:		
Phospholipid04	
Acid soluble08	
Nucleoprotein003	

There is no evidencee that cells can distinguish radio-phosphorus (atomic weight of 32) from non-radioactive phosphorus (atomic weight of 31).

Discussion. At the beginning of the study it was hoped that a comparison of the findings between similar cells of the patients, particularly the white blood cells in the three types of disease, would be possible if correectons for body weight and dosage of P^{32} and P^{31} were made. The findings of one case (Wer) who had received the same quantity of P^{32} by different routes indicated that the factor of route administration would have to be considered also. However, before such comparisons could be possible, among other factors, the metabolic rate and the total volume of the circulating blood elements studied would have to be known. Therefore comparisons of findings between the patients reported here are impossible.

Summary. 1. Therapeutic doses of radio-phosphorus (P^{32}) were administered to 1 patient with lymphoid leukemia, 1 with myeloid leukemia and 2 with polycythemia.

2. The largest portions were retained in the "acid-soluble" fractions of red blood cells, white blood cells and plasma of patients with leukemia and polycythemia 4 to 96 hours after the administration. The peak of retention occurred 12 to 24 hours after administration.

3. In the red blood cells, the level of retention of P^{32} in the "nucleoprotein" fraction reached a peak before the 48th hour and then declined, while that of the "phospholipid" fraction increased constantly, at least until 21 days after administration. In the white blood cells, the levels of retention in both the "phospholipid" and

"nucleoprotein" fractions constantly increased during the period of 96 hours but not for 21 days. In the plasma, the "phospholipid" levels of retention increased and the "nucleoprotein" levels decreased during the same period in general.

4. The concentration of P³² in the various fractions reached higher levels following its intravenous than its oral administration.

5. Comparison between the findings in the three types of disease was not possible because of the undetermined effect of such factors as route of administration, metabolic rate and total blood volume.

6. These findings indicate that, of a quantity of phosphorus (P³¹) ingested by humans, various amounts are absorbed and excreted by the circulating red blood cells, and that the peak of exchange occurs between 12 and 24 hours after consumption. A similar exchange takes place in the circulating white blood cells, which, however, retain phosphorus in the "phospholipid" and "nucleoprotein" fractions for much longer periods and in greater quantities than the surrounding red blood cells. The plasma also has a specific rate of phosphorus exchange. The characteristic trends of exchange of phosphorus in various fractions of the red blood cells, white blood cells and plasma are similar in the 4 patients in spite of the different disease processes involved.

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MAY THE DISEASE COMPLEX THAT INCLUDES MEGA-ESOPHAGUS (CARDIOSPASM), MEGACOLON AND MEGA-URETER BE CAUSED BY CHRONIC VITAMIN B₁ DEFICIENCY?

By EDUARDO ETZEL, M.D.,

FELLOW OF THE JOHN SIMON GUGGENHEIM MEMORIAL FOUNDATION IN THE UNIVERSITY OF MICHIGAN, DEPARTMENT OF SURGERY, SECTION OF THORACIC SURGERY, ANN ARBOR, MICH.

(From the Department of Pathological Anatomy of the Medical School of the University of São Paulo; the Clemente Ferreira Tuberculosis Institute, São Paulo, and the Santa Casa Hospital, São Paulo, Brazil.)

MEGA-ESOPHAGUS (so-called cardiospasm) and megacolon are very common conditions in certain parts of Brazil and have been studied there from various angles for many years. The knowledge thus gained concerning them has enabled us to form concepts on the subject which are practically unknown elsewhere.

We have strong evidence that mega-esophagus, megacolon, pyloric achalasia (pylorospasm), mega-ureter, alterations in gastric chemistry and electrocardiogram with associated polyneuritis and low metabolic rate, are probably varied manifestations of a degener-

ative disease of the autonomic intramural nervous system caused by a chronic deficiency of vitamin B₁. A study of the diet of the patients revealed considerable evidence in favor of this concept of the disease.

Our personal clinical experience is based upon a study of 170 cases and our pathologic studies upon 16 autopsies. The studies of the geographic distribution of the disease is based on 626 cases, 549 of them on record at the Santa Casa de São Paulo during the last 18 years.

For purpose of clarity let us consider first the evidence in favor of a single fundamental pathogenesis, and, second, the evidence which points to a chronic B₁ deficiency as the etiologic factor.



FIG. 1.—Case 1. Enormous megacolon, mega-esophagus of small dimensions and ureters with evident stasis.

Clinical evidence has progressively been accumulated in the literature tending to demonstrate that mega-esophagus and megacolon are related manifestations, possibly of common etiology, and permits expansion of this concept to include other associated morbid findings (Figs. 1, 2, 3).

Neiva and Penna²¹ called attention to the association in the same individual of mega-esophagus and megacolon. Hurst^{9,11} attributed to mega-esophagus and megacolon a common pathogenesis, namely, achalasia of the respective sphincter. Correia Neto^{5a} found that mega-esophagus and megacolon are present concomitantly in 63% of 22 cases studied.

Pylorospasm, or more correctly, achalasia of the pylorus, has been described in association with mega-esophagus and with

megacolon in adults³⁴ and infants. Lehmann¹⁶ considers pylorospasm as an equivalent of mega-esophagus and megacolon. Correia Neto^{5c} observed 5 cases of achalasia of the pylorus in adults with concomitant mega-esophagus and megacolon.

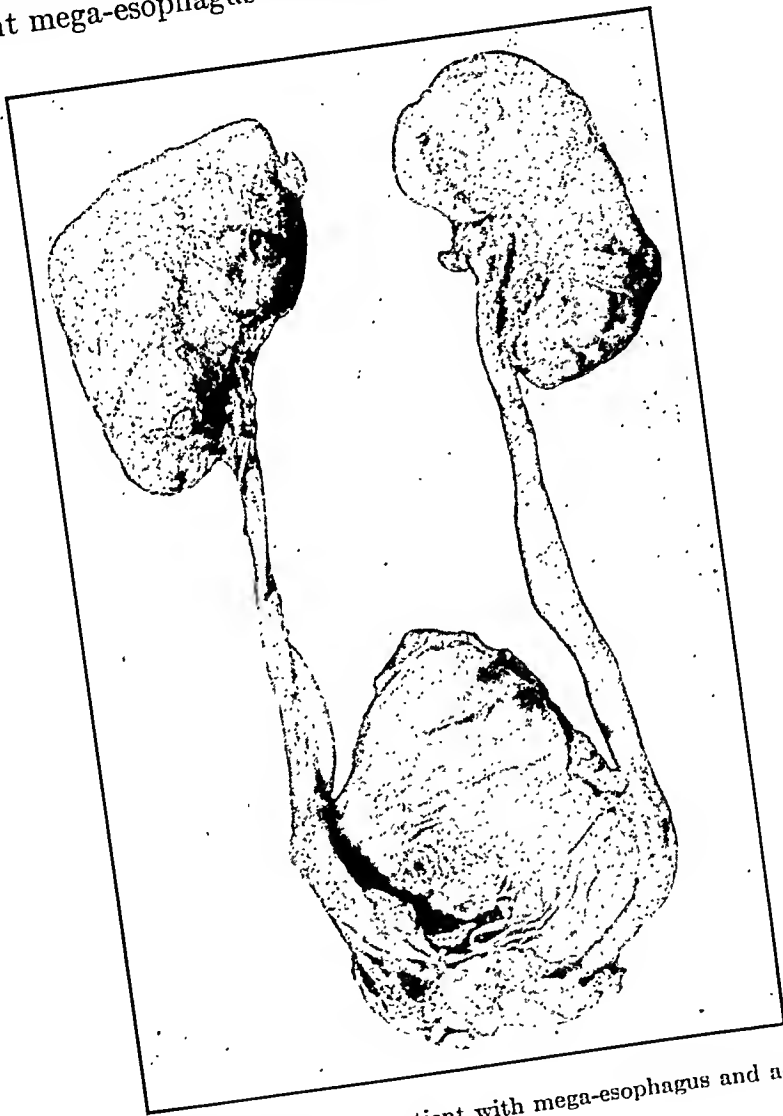


FIG. 2.—Double mega-ureter in a patient with mega-esophagus and achalasia of the pylorus.

Hurst and Jones¹⁰ included mega-ureter under the same pathogenesis of mega-esophagus and megacolon; this view was later adopted by Lehmann.^{16,22} We observed^{8c} this association in 3 out of 16 autopsies on patients with mega-esophagus. Mega-esophagus, achalasia of the pylorus, double mega-ureter with hydronephrosis and hypertrophy of the bladder were present together in one case (Fig. 2); in the second, there was mega-esophagus, megacolon, unilateral mega-ureter and hypertrophied bladder; in the third, there was megacolon with unilateral mega-ureter. The similarity

of the digestive and urinary tracts considered anatomically and functionally is very striking since both possess smooth muscle, several involuntary sphincters, and are innervated by a comparable intramural autonomic nervous system.

The presence of such sphincters in the digestive tract is unquestioned(Aloj¹). Although there may be some argument concerning the exact location of alleged sphincters in some segments of the digestive and urinary tracts, there is no doubt of the existence of specialized function in these areas. The cardia, pyloric, pelvic-rectal and internal anal sphincters in the digestive tract and the pyelo-urethral, urethra-vesical and internal vesical in the urinary tract are all commonly accepted. Clinical and radiologic obser-



FIG. 3.—Case of mega-esophagus (A) and left pelvic dilatation (B) with excretory pyelography.

vation brings out the fact that dysfunction in any areas with sphincteric function produces dilatation proximally.

Hurst^{9,10,11} suggest that the primary factor in the pathogenesis of mega-esophagus, megacolon and mega-ureter is achalasia of the sphincter, that is, absence of the sphincter relaxation which normally occurs on the arrival of the peristaltic wave. Simple absence of normal relaxation without any added spasm of the sphincter is sufficient to prevent the uninterrupted passage through the sphincter. This theory is now accepted as demonstrated by repeated confirmations.^{2,4,6,8a,b,f,22,25}

This sphincteric dysfunction establishes a functional obstruction resulting in stasis above it. There follows, of course, a compensatory

change represented by increased peristalsis of the proximal segments going on to hypertrophy of the musculature. Thus the circular muscle of the esophagus, of the pylorus, and of the colon may become 3 to 4 times thicker than normal, the hypertrophy being required to overcome the sphincteric inertia. Notwithstanding this fact, the sphincter itself does not hypertrophy. This observation is based on the autopsied cases and is in accord with the theory of achalasia proposed. As these changes continue, a state of decompensation is reached when the hypertrophied musculature is no longer capable of overcoming the sphincter inertia. Then, the period of dilatation is initiated and with this, the symptoms usually make their appearance. The process culminates in atony and extreme degrees of dilatation.

The intramural autonomic nervous system extends throughout the entire digestive and urinary tracts. In the digestive tract it is formed by Meissner's plexus, in the submucosa and Auerbach's plexus in between the circular and longitudinal muscular coats. The latter plexus is made of nerves and ganglion cells of two types; multipolar cells (Type 1) and unipolar cells (Type 2 of Dogiel). The cells of Type 1 are motor in function and belong to the vagal and sacral autonomic system. The cells of Type 2—according to Dogiel's theory—should produce the peripheral reflexes of the intestinal wall.

The disposition of these cells in the alimentary tract is of great importance. The esophagus has cells of Type 1 only. In the stomach the cells of Type 2 are first seen near the pylorus. From there onward their number increases; in the jejunum they are abundant but the largest number is seen in the ileum, where the proportion compared with Type 1, is 50%. From the cecum onwards, the disposition is changed; again the multipolar cells (Type 1) begin to predominate and in the rectum, as in the esophagus, only cells of Type 1 occur. The esophagus and the rectum thus have a similar autonomic innervation.^{12-15,18,20,26}

An interesting point demonstrated in our autopsied cases is the relation between the sphincters of the digestive tract and the cellular components of Auerbach's plexus. Directly above the sphincter there are many more cells than elsewhere in the alimentary tract.

The intramural autonomic nervous system of the ureter and bladder is made up of the same type of cells.³⁰

I described the finer neuropathologic alterations of Auerbach's plexus in mega-esophagus in 1934.^{5a,b,f} The methods used were those of Bielschowsky-Gross for the neurofibrillar apparatus and Nissl's for the study of the nerve cells. The alterations of the cells were dislocation of the nucleus to the periphery, central chromatinolysis, micro-vacuolization and degeneration of the protoplasm. Bielschowsky-Gross's method showed pyknosis of the nucleus,

expulsion of the nucleus, destruction of the neurofibrillar system and neuronophagia. The alteration of the axis-cylinder can be classified as cleavage, retraction balls of Cajal, argentophilia and thickening and fragmentation of the axis-cylinder (Figs. 4 and 5).

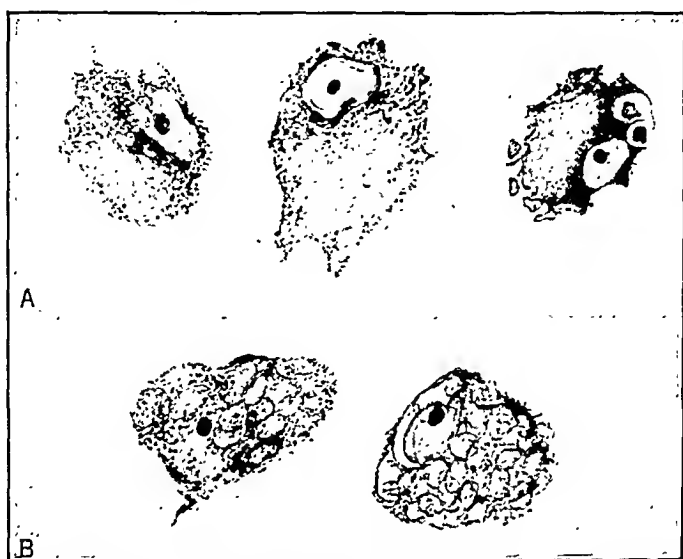


FIG. 4.—Mega-esophagus, lower third of the esophagus. *A*, Cells of the plexus of Auerbach with central chromatolysis; *B*, cells of the plexus of Auerbach with vacuolization and degeneration of the cytoplasm. (Nissl's stain.)

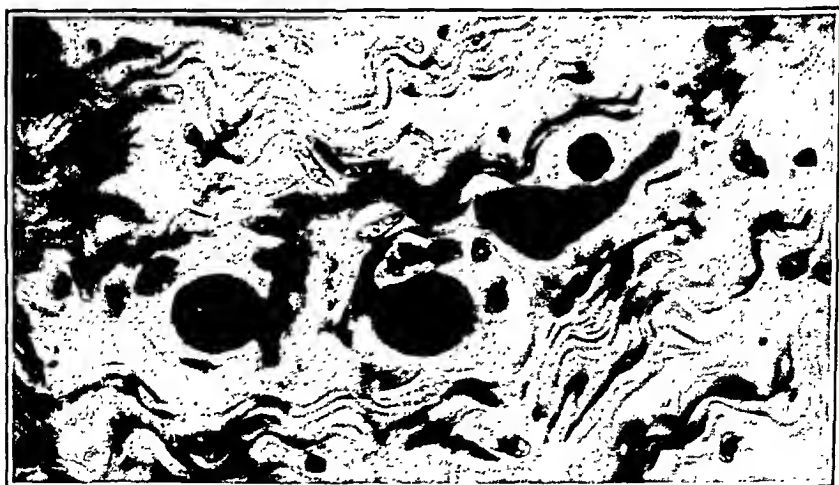


FIG. 5.—Mega-esophagus, lower third of the esophagus. Retraction balls and cleavage of axis cylinder. (Bielschowski-Gross's stain.)

Investigating a case of advanced bilateral mega-ureter, I was unable to even find the intramural nervous elements. These lesions

are typically degenerative. In order to demonstrate that they are not secondary to the mere dilatation with consequent rupture of these elements, the cardia of dogs was partially occluded by ligature. This resulted in dilatation of the esophagus, but even after 4 months the plexus was found to be quite normal.⁸⁰

We believe this degeneration is the result of a selective acting agent and thus is primary in type and not secondary to some factor influencing the entire involved organ.

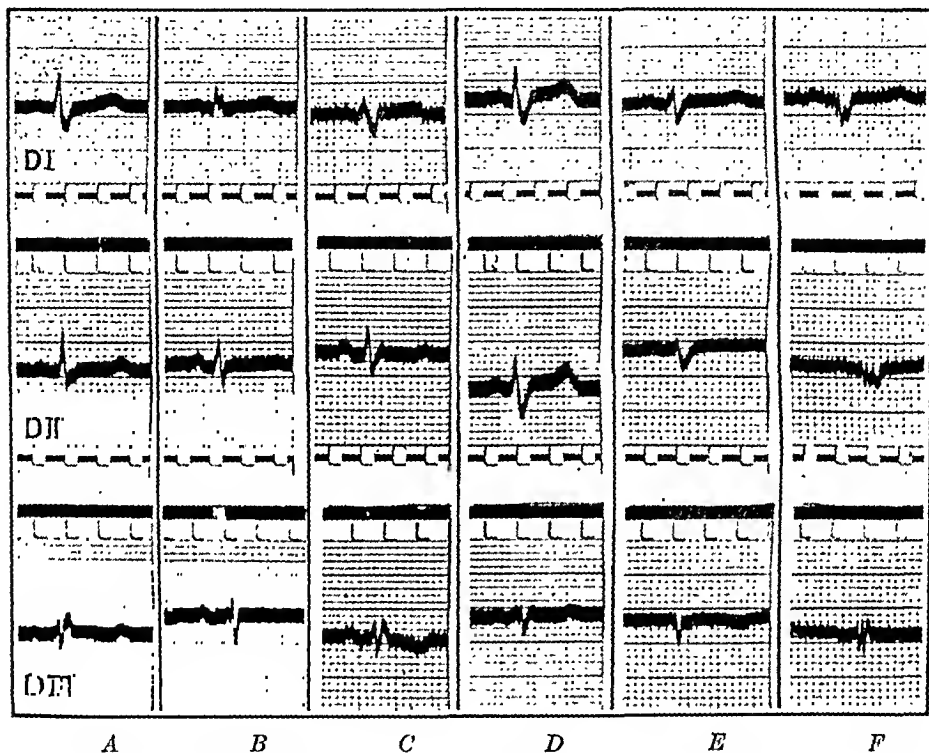


FIG. 6.—Electrocardiograms of 6 cases of: A-B-C, mega-esophagus; D-E, megacolon; F, mega-esophagus and megacolon.

Faced by these facts, it seems but a naturally logical step to visualize all of these manifestations as being produced by the same fundamental etiology, that is, the destruction of the intramural autonomic system. Further, the hearts of such patients also becomes injured. Neiva and Penna²¹ called attention to the frequent complaint of palpitation in cases of mega-esophagus and megacolon. Sterling²⁷ and Villela³³ described electrocardiographic alterations in cases of mega-esophagus but failed to correlate these with other morbid findings.

Studying 24 unselected cases of mega-esophagus or megacolon or both conditions occurring concomitantly, we^{8c,8d} found electrocardiographic alterations in 70.8% of the cases (Figs. 6 and 7). These patients were almost always younger than middle-age and did not complain of cardiac symptoms. A slow pulse rate was 6 of

frequent occurrence.⁸⁷ Other investigations subsequently brought out confirmatory evidence of this primary report. Thus, Ramos²⁷ studied our 24 cases mentioned, added 7 other cases, and made clinical observations showing that these alterations of the electrocardiogram consist of disturbance of the conductive system; the electrocardiogram shows disturbances from the simple prolongation of the *QRS* complex to bundle-branch block. Ramos concluded that the destruction of the autonomic nervous system of the heart could explain the alterations of the electrocardiogram. Vasconcelos and Botelho³² investigated the autonomic nervous system of the heart in cases of mega-esophagus having electrocardiographic changes and could not find even traces of this nervous system. Ramos and Oria,²⁴ in the hearts of my autopsied cases of mega-esophagus and megacolon, were able to demonstrate destructive

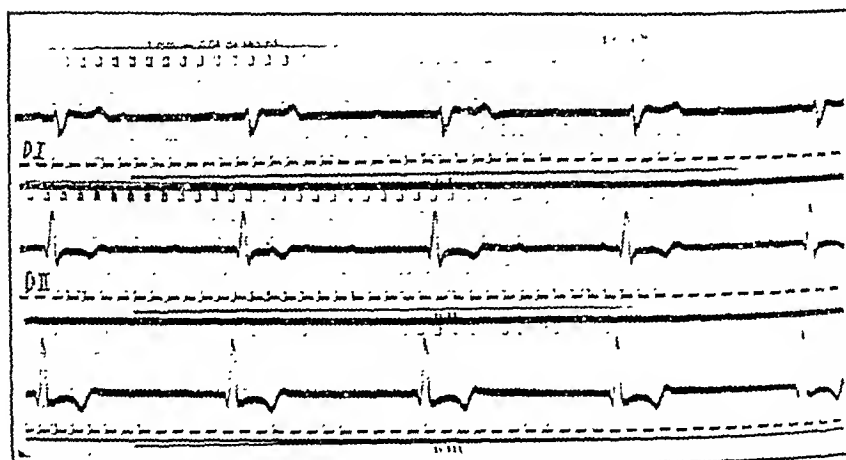


FIG. 7.—Case 1. Electrocardiogram showing partial *a-r* and bundle-branch block.

lesions in the autonomic intramural system in cases with typical electrocardiographic changes.

Since the autonomic nervous system of the heart can be regarded as at least the equivalent of the plexus of Auerbach in the digestive tract and intramural plexus of the urinary tract, these changes can be visualized easily as being of the same nature.

Vampre³¹ described the absence of the patellar reflex in patients having mega-esophagus. The patellar and Achilles reflexes may be diminished or absent. In severe cases the disturbances in the reflexes are generalized. The interpretation of this disturbance is obscure. It is called polyneuritis because it has a certain resemblance to the symptoms of classical polyneuritis. However, it is only by routine examination that this disturbance of the reflex is found, since it is rarely a source of symptoms.

Gastric chemical studies were made in 15 cases^{8c} (9 mega-esophagus, and 6 megacolon). We found hypochlorhydria in 9 cases and achlorhydria in 2 cases. The Katch-caffein test was used in the determination of free hydrochloric acid; the histamine test was used in the cases of achlorhydria.

Correia Neto^{5b} in a series of 22 cases of mega-esophagus and megacolon pointed out the presence of low metabolic rate in 40.7%.

The morbid association of mega-esophagus and megacolon can hardly be regarded as accidental. The autonomic nerve supply to all of these organs is so similar that it seems likely that a common factor is responsible for the functional disorder of them all. This led me (February, 1935)^{8c,d} to regard mega-esophagus and megacolon as a manifestation of a diseased condition of the autonomic nervous system, the complete or partial destruction of which would result in the appearance of some or all of these associated disorders. This theory suggests that we are not dealing with several independent affections but with one that has varied manifestations.

Analysis of Cases. Substantiating the previous discussion, Table 1 illustrates the frequency with which these varied manifestations occur. This group of 29 cases were studied systematically for the lesions listed. Although other manifestations of the disease were not routinely sought, mega-ureter was found in 5, achlorhydria in 2, hypochlorhydria in 1, low metabolic rate in 3, and achalasia of the pylorus in 2.

TABLE 1.—THE RELATIVE FREQUENCY OF THE MANIFESTATIONS OF THE DISEASE IN 29 CASES.

Manifestations of the disease.	No. of cases. %.	Morbid associations.			
		Mega-esophagus.	Mega-colon.	Alterations, EKG.	Alterations peripheral reflexes.
		%.	%.	%.	%.
Mega-esophagus .	23—78	23—100.0	13— 56.5	13— 56.5	9— 39.1
Megacolon .	19—64	13— 68.4	19—100.0	12— 63.1	3— 15.7
Alt. of EKG .	18—62	13— 72.2	12— 66.6	18—100.0	6— 33.3
Alt. of peripheral reflexes .	9—31	9—100.0	3— 33.3	6— 66.6	9—100.0

The typical picture of these patients is exemplified in the 3 case reports.

CASE 1.—J. S., aged 22, negro, Brazilian farm laborer, 6 months before we saw him, began to have constipation with 2 or 3 days between evacuations. This disturbance became progressively worse and after 2 months the feces were expelled in hard fragments, the intervals between evacuations increasing. He had not had a stool in the previous 15 days. At the onset, he began to have difficulty in swallowing, as the food seemed to stop near the ensiform cartilage. In this same region pain occurred soon after eating. By taking water the food descended but at times the water was regurgitated, the food passing on to the stomach.

Physical examination showed the apex beat at the 4th intercostal space in the mammary line; a soft systolic murmur was heard throughout the

cardiac area. A tumor of great size was palpated in the central portion of the abdomen and in the left.

Radiologic examinations: Colon: mega-sigmoid (Fig. 1). Esophagus: mega-esophagus of small dimension. Heart: the cardiac area measured 130 cm.² an approximate increase of about 30%. The radiologic aspect is of a general cardiac Ureters: evident bilateral ureteral stasis (by excretory 1).

The electrocardiogram showed total A-V block; bundle-branch block (Fig. 7). The basal metabolism rate was -12%. The Wassermann blood test was negative.

This case presented megacolon, mega-esophagus, ureteral stasis and total A-V block with bundle-branch block.

CASE 2.—J. M., aged 26, white, Brazilian, farm laborer, had had dysphagia for the past 4 years. At the onset there was a marked substernal burning sensation. Five months later dysphagia developed as a sensation of food stopping near the ensiform cartilage, which compelled him to take water during meals. It became worse until the patient needed to drink more and more water in order to force food into the stomach. A year ago he became much worse, drinking great quantities of water during meals, he experienced a sensation of the sudden passage of the food into his stomach. Five months ago he began to regurgitate food and water. There was constipation, the stools being hard and being passed approximately once in 3 days.

Physical examination revealed nothing of particular interest.

Radiologic examination: Esophagus: mega-esophagus; colon: extreme elongation and dilatation of the sigmoid and rectum.

The electrocardiogram showed slight right axis deviation and slurring of QRS.

This case presents colon with moderate symptoms of constipation. The showed only small alterations.

CASE 3.—L. B., ag farm laborer, had constipation of 1 month's duration. Prior to this there had been daily bowel movements and no symptom of the digestive tract disturbance. At the time of patient's admission to the hospital there had been no bowel movement for 2 weeks. During the preceding 2 weeks as many as 5 days had passed without a bowel movement. Discomfort and vague abdominal pains were relieved by the passage of gas. Cathartics had little effect. The abdomen increased greatly in size and seemed to contain a hard tumor.

Examination of the heart showed apex beat at the 3d intercostal space in the left parasternal line; soft systolic murmur at the mitral area; accentuation of the aortic second sound; extrasystoles. A hard tumor more palpable in the central and left portions of the abdomen.

Radiologic examination showed an elongation and dilatation of the colon. The esophagus was normal. The cardiac area was normal.

The electrocardiogram showed arborization block. Auricular extrasystoles transmitted and blocked. Nodal ventricular escape. The basal metabolism was -66%. The Wassermann blood test was negative.

Case with megacolon, severe alterations in the electrocardiogram with negative cardiac clinical findings and low basal metabolism.

Considering the strong evidence in favor of a fundamental etiology for all of the varied manifestations correlated above, a statistical review of 626 cases was made⁵⁴ in an effort to obtain a clue as to the nature of the etiologic agent. From the data collected, several very important points became manifest.

The ages of patients having any one of the above manifestations

of the disease ranged from 2 to 79 years (Chart 1). The greatest number, however, was between the ages of 15 and 25; the majority was admitted before the age of 40 (76.5%).

In 229 of the 626 cases, the age and onset of symptoms were obtained (Chart 2). In 58% of these 229 patients the symptoms began before the age of 25 years and the majority was between 15 and 25 years. Sex apparently had no influence in the age of the onset of symptoms; 89.2% of the patients were white, 79% were males. Farm-hand was the profession in 83% of the male components of this group.

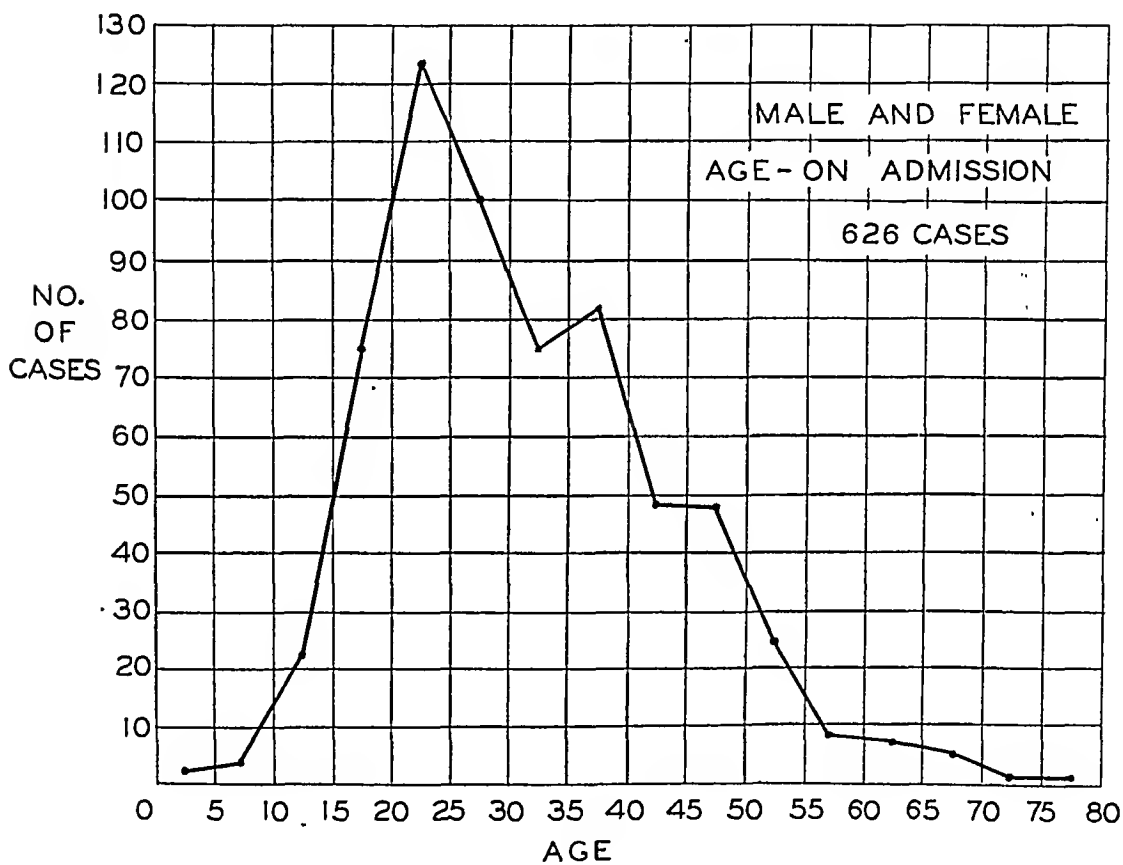


CHART 1.

Thus, the disease occurs by preference in young males from the rural sections.

A more detailed study of the geographic distribution brought out the fact that the majority of the patients come from the rather poor central and northeastern parts of the State of São Paulo. There were no cases from the coastal region. Further, those patients who happened to come from a richer zone in the state were found to have been born in sections of the state or migrated from portions of the country which were poor. There were 58

foreigners included in this group; of these 28 were Italians, 26 of whom came from near Venice where dietary deficiency manifested notably as pellagra is very common.

Thus, there is a strong suggestion that a dietary deficiency may be responsible for these manifestations.

The dietary^{84, i} habits of the people from the zones of the state where the disease is most frequently found are very well known and quite unvarying. The diet consists of beans, polished rice, flour of manioc and crude cane sugar. Occasionally dried meat, eggs, potatoes, vegetable and milk are added. Such a diet is deficient in vitamin B₁.

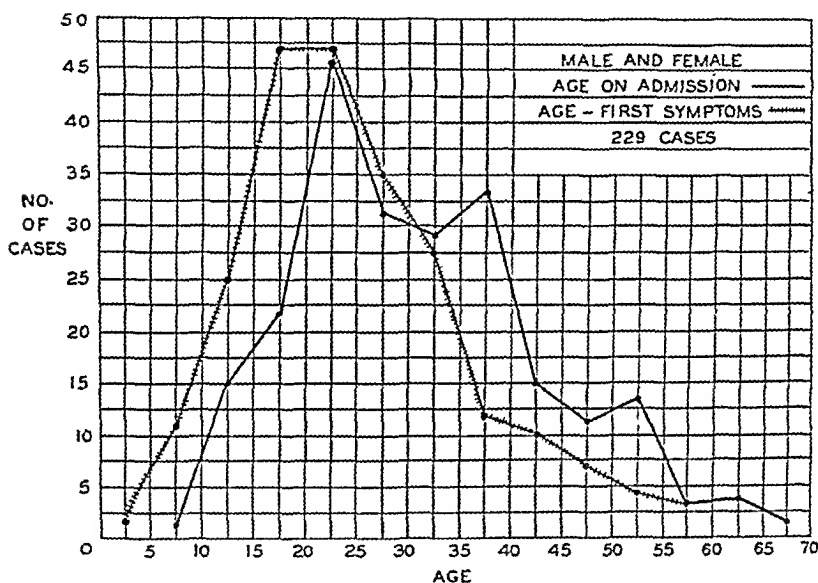


CHART 2.

Comparing beriberi and mega-esophagus with its related manifestations, we^{8d} find that the manifestations of the two disorders are similar. Japanese²⁸ observers report lesions of the autonomic nervous system occurring in beriberi, as we have shown them to occur in mega-esophagus. Digestive disorders such as achlorhydria, vomiting and constipation, and cardiac and peripheral reflex disturbances are also common in beriberi.

The literature dealing with the pathology of vitamin B₁ deficiency indicates that it is frequent in poorly organized diets producing a latent or chronic state of insufficiency. Further correlation has been made between vitamin B₁ deficiency and various morbid conditions such as changes in the plexus of Auerbach (McCarrison^{17a, b}), pylorospasm (Brodie³), obstipation (Montague,¹⁹ Vorhaus, Williams and Waterman³⁶). Further, it has been related to the total caloric intake more especially in predominantly carbohydrate diet which

requires a greater supply of the vitamin B₁ (Cowgill⁷). A lowered metabolic rate (Vorhaus³⁵) and cardiovascular disturbances (Weiss and Wilkins³⁷) have also been correlated with its deficiency. The human diet, even when very restricted, is always varied to a certain extent. By varying the diet, the sources of vitamins are also varied. Not having a constant deficiency of vitamin B₁, but a fluctuating deficiency, the morbid manifestations would be expected to vary accordingly in their degree of intensity.

Thus, we see that the disease occurs predominantly in young males of the laboring classes coming from regions where, for economic reasons, the diets are relatively unvaried and largely composed of carbohydrates and deficient in vitamin B₁. Being young male laborers, their total caloric demands are high. Their diet aside from being relatively deficient in vitamin B₁, is largely made up of carbohydrates and thereby increases the demand for vitamin B₁⁷ (caloric-vitamin ratio of Cowgill). Those found in the more prosperous regions had moved there from the areas where the disease was endemic after a considerable period of latent deficiency.

The degeneration in the plexus of Auerbach is irreparable, and although some symptomatic improvement has been noted when treating these cases with vitamin B₁,^{8i,29} we cannot claim actual regression. Conversely, those patients who develop symptoms in the presence of an adequate diet indicate that although further degeneration may have been prevented by the adequate intake of vitamin B₁, the early changes of stasis or achalasia were present prior to migration, leading to hypertrophy and finally decompensation of the musculature, thus becoming symptomatic. Although no definite data have accumulated concerning vitamin therapy, its use seems justifiable.

Summary and Conclusions. The data presented tend to show that mega-esophagus (cardiospasm), megacolon, achalasia of the pylorus, mega-ureter and disturbances in the cardiac conduction system are but varied manifestations of the same disease. Achlorhydria, low metabolic rate and polyneuritis (peripheral reflex changes) are thought to be in the same clinical picture, even though not as clearly so.

Degeneration in the intramural autonomic nervous system is believed to be the anatomic basis for these manifestations.

A chronic or intermittent deficiency of vitamin B₁ is suggested as the etiologic agent responsible for the degeneration in the autonomic nervous system, thereby instituting a series of physiopathologic changes which culminate in the clinical picture described.

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SPONTANEOUS BERIBERI OF THE MONKEY AS COMPARED WITH EXPERIMENTAL AVITAMINOSIS.

BY C. P. LEBLOND, M.D.,*

AND

J. CHAULIN-SERVINIÈRE, PH.D.,

ASSISTANT IN BACTERIOLOGY, PASTEUR INSTITUTE, CASABLANCA, FRENCH MOROCCO.

(From the Pasteur Institute of Morocco.)

IN 1940, many animals of the monkey colony (*Macacus sylvanus*) at the Pasteur Institute of Morocco showed evidence of a disease never previously observed in this 5-year-old colony. The disease, characterized clinically by an association of polyneuritis and cardiac weakening, and pathologically by cardiac and nervous lesions, was quite similar to human beriberi. A comparison of our sick animals with monkeys fed experimentally-deficient diets appeared convincing enough to explain the disease on the basis of a partial vitamin B₁ deficiency. Our results also provided a basis for general conclusions on the nature of beriberi.

* Now Research Fellow, Departments of Anatomy and Radiology, University of Rochester School of Medicine and Dentistry.

I. CLINICAL AND PATHOLOGIC FINDINGS. *Etiology.* The time of the appearance and the seriousness of the disease were dependent in part on the *age* of the animals. The adolescents, monkeys of about 3 years, were the first to be attacked (Nos. 1 to 6, Table 1). Younger animals, $1\frac{1}{2}$ to 2 years old, exhibited the disease about 3 months after the first adolescent cases. All the adolescents and 7 out of the 20 young were attacked. In the affected young and in most adolescents the disease progressed to a fatal termination unless properly treated.

Of the 22 adults kept in the main room of the colony with the adolescents, only 1 was ill, with mild chronic symptoms (No. 30). In this room, ventilation, light, temperature and cleanliness were quite satisfactory. Two other adults kept in a smaller room, less well lighted and not regularly supervised, also showed chronic symptoms of the disease (Nos. 31 and 32).

Sex did not seem to influence the disease. The *species* might have played a rôle, since 2 Cercopithecids (*Æthiops sabæus*) in the same cage as the 2 sick adult macaques remained in perfect health.

Symptoms. After an insidious beginning the disease evolved irregularly, showing alternate periods of improvement and aggravation, generally ending in death within a few weeks to several months. The course of the disease could usually be divided into a prolonged phase characterized chiefly by neuromuscular disorders, followed by a terminal phase of acute dyspneic symptoms.

The earliest disorder noted was the animal's inability to leave the ground when preparing to jump. Climbing became clumsy, the gait unsteady, and the reduced activity caused the animals to remain seated in the cage most of the day (Fig. 1, *a*). As the disease progressed, the resting animal assumed a characteristic sitting posture with the lower limbs bent up in front and the head resting on the knees. It raised itself with difficulty, while standing appeared painful and became gradually impossible. The attempts to walk showed first a limping with a frequent unilateral predominance, that subsided while both sides became paralyzed and the animal could no longer keep its balance. A characteristic gait was observed in 2 cases, and suggested by many others: the animal moved the lower half of its body in one block, as if the lower limbs were fixed to the pelvis; when walking it would lean on the upper limbs to propel itself, using its arms as crutches. Muscular strength was much diminished, especially at the lower limbs. The animals had almost complete use of their upper limbs; some could even climb, hoisting themselves by their arms. In the 2 cases in which the evolution of the disease was experimentally accelerated (Nos. 9 and 10, Table 3), the paralysis extended to all four limbs. There was also a case of left facial paralysis (No. 6). When testing the muscular strength of the animals, it was noticed that they kept their lower limbs flexed, being unable to extend them. There

seemed therefore to exist some degree of muscular contracture. Muscular atrophy was marked. It predominated in the lower limbs and the pelvis. The muscles of the trunk (Fig. 1, *b*) and of the arm were involved too, although to a much less degree. However, in spite of the intense atrophy, electrical stimulation of the muscles showed no reaction of degeneration.

TABLE 1.—SPONTANEOUS BERIBERI.

Animal No.	Sex.	Body weight		Approximate age, yrs.	Date of apparent beginning (1940).	Approximate duration, mos.	Hind leg paralysis.	Hind leg muscular atrophy.	Knee jerk.	Dyspnea.	Pulse.	Observations.
		Beginning, kg.	Death, kg.									
1	F	3	Mar.	2	+++	+++	Dead, Apr. 23.
2	?	3	Mar.	2.5	+++	++	Dead, May 15.
3	F	2-3	Apr.	3	+++	++	Absent	+	..	Dead, July 4.
4	M	..	2.06	2-3	Apr.	3	+++	+++	Absent	+	..	Sacr., July 10.
5	F	..	2.48	3	Apr.	3	+++	+++	Weak	+	165-110	Dead, July 22.
6	F	3.14	2.48	3	Apr.	6	+++	++	Weak	+	220	Sacr., Sept. 21.
7	F	3.48	..	3	July	3	++	=	Normal	+	225	Treat. Bi, Sept.
8	F	4.14	..	3.5	July	3	+	-	Normal	-	200	Treat. Bi, Sept.
9	M	3.60	..	3.5	July	..	=	-	Normal	-	250	See Table 2.
10	M	4.27	..	3.5	Aug.	..	+	-	Normal	-	..	See Table 2.
11	M	..	1.80	2	Aug.	1.5	+++	=	Weak	+	170	Dead, Sept. 7.
12	M	..	1.30	2	Aug.	1.5	+++	=	+	..	Dead, Sept. 9.
13	M	1.51	..	1.5-2	Sept.	..	+	+	Absent	+	180	Treat. Bi, Sept.
14	M	2.08	..	1.5-2	Sept.	..	=	-	Weak	+	180	Treat. Bi, Sept.
15	F	1.91	1.20	1.5-2	Sept.	1	-	-	Weak	-	..	Treat. Bi, Sept.
16	M	1.85	1.75	1.5	Aug.-Sept.	1.5	++	=	Absent	+	..	Dead, Oct. 7.
17	F	1.38	..	1.5	Aug.-Sept.	..	++	=	Absent	+	180	Treat. Bi, Sept.
30	M	6.80	..	Adult	Mar.	7	++	+	Normal	-	320	Treat. wheat germ.
31	M	7.93	..	Adult	Apr.	6	++	++	Normal	+	190	Treat. Bi, Sept.
32	F	3.48	..	Adult	Apr.	6	++	++++	Weak	-	160	Treat. wheat germ.

Disturbances of the reflexes were variable. The knee jerk, normally pronounced in monkeys, sometimes appeared exaggerated at the beginning of the disease. In well-characterized cases, the reflex weakened gradually and finally disappeared. However, death would sometimes occur without complete abolition of the knee jerk (No. 6). The cutaneo-plantar reflex (Babinski sign) occurred in flexion as in normal animals.⁵ Some degree of photophobia was found in 2 cases before death (Nos. 9 and 10). Disturbances of sensitivity were not well defined: there seemed to be some hypoaesthesia of the lower limbs. Pain was apparently not present.

In the youngest monkeys the disease was revealed by acute attacks of *contractures* which usually lasted several minutes or (in 1 case) a few hours: the fingers were maintained flexed on the palms and the hands flexed on the forearms, with sometimes the aspect of wrist-drop. In only 1 case were there also painful cramps. Sometimes these attacks of contracture complicated a more or less

marked paralysis of the lower limbs (No. 13); sometimes they occurred in animals otherwise nearly normal (Nos. 14 and 15).

Cardiac disturbances manifested themselves at the beginning by a slight dyspnea when at rest and by more and more violent attacks of dyspnea occurring as a result of strain or emotional stress. The face was cyanotic. In younger animals, the increase in the number and amplitude of respiratory movements determined a deformity of the thoracic cavity which little by little produced a marked anterior prominence.

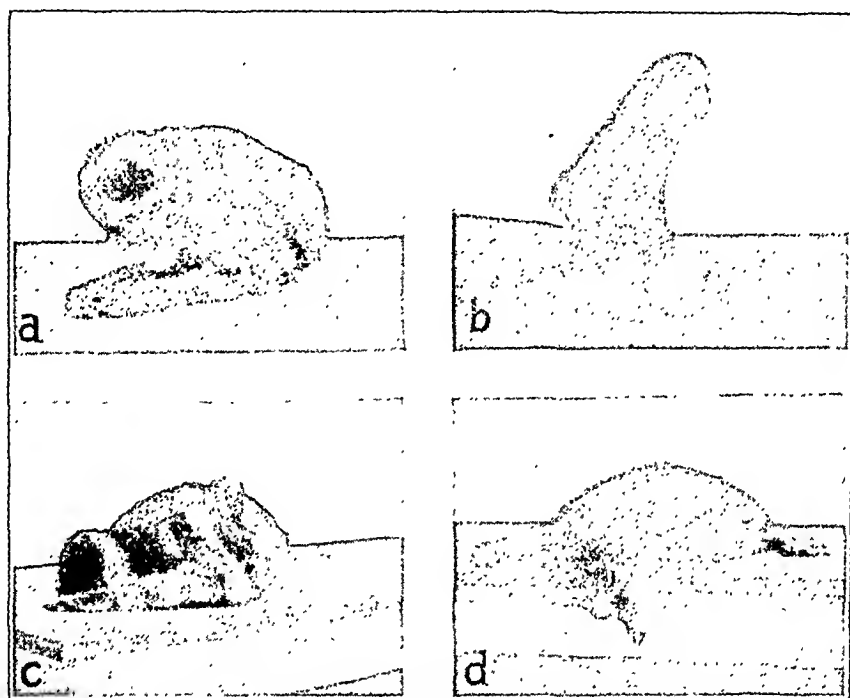


FIG. 1.—Above, two monkeys at the beginning of the disease, Nos. 4(a) and 5(b). Below, two monkeys at the terminal period, Nos. 6(c) and 9(d).

The pulse slowed down gradually as the disease progressed. Instead of 250 pulsations a minute as in the normal animal, one found a gradual diminution to 180 and even to 150 or less. Auscultation of the heart revealed sounds less defined than normally, with sometimes extrasystoles in the terminal phase. Cardiac symptoms predominated in 2 young animals (Nos. 16 and 17) in which the paralysis of the lower limbs was slight. The cardiac phenomena were much accentuated, especially the attacks of dyspnea that caused the death of 1 animal (No. 16).

The general condition of the animal became aggravated little by little. Besides muscular atrophy, there was emaciation of the whole body. The activity of the animal was restricted and the playfulness of the animals disappeared. The appetite decreased. No fever was observed.

The transition to the *terminal period* was progressive, but could be accelerated by emotional stress, such as occurred during clinical examination or any handling that determined marked reactions of the monkey. The animal was then no longer able to sit up or to walk, but lay with the head resting on the upper arms stretched in front of him (Fig. 1, c and b) or hunched in a ball with the head resting on the lower limbs. Besides a more flaccid paralysis the animals sometimes showed sudden shuddering or quivering localized in certain muscular groups (No. 11, Table 1; also 9 and 10, Table 3). By that time, cardiac disturbances increased. Attacks of dyspnea were more frequent and violent. The immobile animal ate very little or not at all; sometimes it had diarrhea and in 1 case, vomiting. Finally death occurred as a result of cardiac failure or cachexia. This end-phase lasted about 10 days.

Autopsy Findings. The nerves were examined in all but 3 cases by Marchi's and Weigert's methods (modifications of Nageotte and Spichneier). Characteristic Wallerian degeneration of the myelin sheath was found. While some fibers appeared normal or showed only foamy degeneration of the myelin, the disintegration was usually marked, extending frequently to the axone with a transformation of the myelin into irregular fatty droplets. The lesions predominated in the peripheral nerves, for instance the plantar nerve. In the main nerves, a comparison of the sciatic nerve as it emerged from the sacro-lumbar plexus with the ulnar nerve coming out of the brachial plexus showed a predominance of the lesions in the nerve of the lower limb. In monkey No. 6, with the facial paralysis, degeneration was found in the facial nerve on the stricken side. In every case examined, the vagus nerve was markedly attacked. On the whole, the lesions greatly exceeded those reported in classical descriptions of acute polyneuritis of the pigeon (Bertrand *et al.*).

There was no evidence of subcutaneous edema, but about 2 cc. of watery fluid was consistently present in the pericardial cavity. The heart was frequently hypertrophied. Three young animals dying of dyspnea presented an unusual deformity due to the expansion upward and forward of the anterior thoracic walls, causing the lower ribs to impress deep grooves on the upper part of the liver and the liver itself to herniate through the substernal attachment of the diaphragm in the form of small pediculated expansions about the size of a cherry. Frequently, pulmonary infarcts of various ages were found, probably as a consequence of right cardiac insufficiency.

The digestive tract showed signs of general atony, with abnormal distention of some segments of the small intestine and colon. Congestion was manifested by diffuse redness and ecchymotic points along the digestive tract; which occasionally appeared as well-formed ulcerations, especially in the pyloric region of the stomach. Mesenteric lymph nodes were greatly enlarged. Fatty degeneration

of the liver was frequent. The thymus glands were completely atrophied.

The genital activity slowed down. Histologic examination of the gonads showed no sperm formation in the adolescent males. All the females of the colony ceased menstruating and bearing young before the appearance of the first symptoms of paralysis.

Conclusions From Clinico-pathologic Observations. This incomplete and seemingly painless paralysis, with decrease of tendon reflexes save for the Babinski sign, suggested the existence of a polyneuritis. Since no symptom of intoxication or infection was found and the disease could not be transmitted by inoculations of blood or nervous tissue, the polyneuritis was ascribed to a dietary deficiency, namely beriberi. This diagnosis was confirmed by the heart disturbances, and the autopsy findings of hydropericardium and nerve degeneration.

II. STUDY OF THE DIET. Before September, 1939, the monkeys were in good health while given a diet of acorns supplemented with small amounts of stale bread, carrots, cabbages and sometimes sunflower seeds. When the war started, fresh acorns could not be obtained. The animals were given stale acorns which had been stored for a year and were spoiled to the extent that the substance of some of them was transformed into pulverized material. In February, 1940, the supply of acorns was exhausted. From that time on, the monkeys were given: 1, noodles or semoule (white barley meal), cooked alone or with chick peas and broad beans, these two latter given semi-weekly or less often; most of the monkeys ate little of or refused this paste as they dislike cooked food; 2, a small quantity of either carrots, or turnips or cabbage leaves, and 3, stale white bread *ad libitum*. Two months after this diet had been started, the first cases of beriberi appeared.

In Table 2, a tentative estimate of the amount of thiamin absorbed by the animals will be found. It could be only a rough estimation as the animals ate variable amounts of each item and there were variations in the diet according to the vegetables available. Finally, the figures for bread were possibly too high, for in Casablanca it was thoroughly bleached.

TABLE 2.

	Thiamin content (after Williams ¹¹) in gammas per gm.	Approximate amount eaten daily, gm.	Thiamin ingested daily, gamma.
Noodles5	5	2.5
Semoule1	5	.5
Chick peas	1.5	1	1.5
Broad beans	2.5	1	2.5
Carrot4	9	3.6
Turnip5	2	1.0
Cabbage2	7	1.4
White wheat bread5	20	10.0
Total	---	50	23.0

The requirement for thiamin was shown by Arnold in Elvehjem's laboratory^{1,2} to be about 75 to 100 gamma of thiamin per 100 gm. of a low fat diet. This requirement was similar in all species studied, including man. In our monkeys' diet there were only 46 gamma of thiamin per 100 gm. of food.

From this dietetic history it may be concluded: 1, that the disease was not a toxic polyneuritis due to the damaged acorns, as the first symptoms were observed 2 months after the interruption of the acorn diet; and 2, that the diet was such as to produce a partial vitamin B₁ deficiency.

Comparison of the Observations With the Effects of Experimental B Deficiency. Because of the contrast between the numerous symptoms in human beriberi and the paucity of signs in the experimental B₁ deficiency observed in animals, there has been a general reluctance to hold the lack of thiamin as the only cause of beriberi.⁹ Since the spontaneous beriberi of the monkey was polysymptomatic, as in humans, experiments were planned to determine whether an experimentally induced B₁ deficiency would also bring forth a similar nervous and cardiac syndrome. In a monkey given a diet of unwashed polished rice, as reported by Shiga and Kusama,¹⁰ nervous and cardiac disturbances were strikingly similar to those of our cases of spontaneous beriberi.* On the contrary, in McCarrison's experiments, the monkeys died rapidly without outstanding symptoms.⁶ In this case, the rice used for the diet had been completely deprived of thiamin by a sojourn of 36 hours in the autoclave.

TABLE 3.—EFFECT OF B-DEFICIENT DIET.

Animal No.	Sex.	Body weight.		Supplement.	Clinical symptoms at end of deficiency.				Cessation of diet.	Autopsy pericardial fluid, cc.
		Before, kg.	Death, kg.		Nervous symptoms.	Diarrhea.	As-thenia.	Pulse.		
21	F	5.14	4.48	None	+++	+++	150	Dead, 33 d.	.5
9	M	3.60	2.90	Quadrilegia, no reflexes	+	+++	158	Dead, 8 d.	1.5
10	M	4.27	Quadrilegia, no reflexes	+	+++	180	Dead, 6 d.	2.5
24	F	1.99	1.82	None	—	+++	..	Dead, 40 d.	—
23	M	2.57	..	0.1 mg. B ₁ semi-weekly	None	—	—	..	Interruption after 14 wks.	—
25	M	2.67	..	10 mg. B ₁ semi-weekly	None	—	—	..	Interruption after 9 wks.	—

The diet given to our experimental monkeys was practically devoid of thiamin, since prolonged washing of the rice was shown by Spruyt¹¹ to reduce its thiamin content from 0.5 to 0.02 gamma per gram. The results (Table 3) indicated that, contrary to the controls maintained in good health (Nos. 23 and 25), the deficient adult (No. 21) and young (No. 24) died in 33 and 40 days respec-

* One case was also briefly reported by Schaumann.⁸

tively with very few symptoms. Histologic examination of the nerves (No. 21) showed only a minute foamy degeneration of the myelin. Therefore, as in McCarrison's cases, a *complete* thiamin deficiency had resulted in death before any prominent nervous or cardiac symptoms could appear, while the *partial* thiamin deficiency of the regular colony diet (and of Shiga and Kusama's case) had produced a chronic beriberi with multiple signs. Recently, several reports indicated that more numerous clinical or histologic symptoms were also observed in rat,⁷ pigeon^{13,14} and dog,¹² when the B₁ deficiency is not complete.

In the case of monkeys Nos. 9 and 10, they were the only adolescents of the colony that were not severely ill (Table 1) when they were given the experimental diet.* The effects of the diet were unusually rapid, since after 6 days (No. 9) or 3 days (No. 10), a sudden and complete flaccid quadriplegia set in, with muscular twitching and photophobia, resulting in death within 3 or 4 days. This rapid outburst of paralytic symptoms implied that these adolescents had no store of vitamin B₁, due to the fact that while on the colony diet they had used up more of the vitamin than younger (No. 24) and older (No. 21) animals. This confirmed the greater susceptibility of the adolescents to beriberi, as indicated in the section on the etiology of the disease. This acute outburst of beriberi strikingly recalls the "fulminating beriberi" observed in humans.¹⁷

In short, B₁ deficiency is either (a) *complete*, resulting in rapid death with few or no previous specific symptoms; (b) *partial*, resulting in beriberi; (c) partial at first, and suddenly complete, resulting in beriberi fulminans.

Therapeutic Assays. For the last 2 months (September and October, 1940) the monkeys of the colony, as well as 2 sick animals (Nos. 30 and 32) were given a handful of a thiamin-rich mixture of equal volumes of barley and wheat germ, in addition to their usual food. No new cases of beriberi have since appeared and the females began menstruating again.

Cure of sick monkeys with pure thiamin† (5000 to 50,000 ganmas daily) failed in 3 animals at the terminal period. The lesions were probably too far advanced and the emotion due to subcutaneous

* The following diet was given *ad libitum*: Polished and washed rice, 87%; wet casein, 10%; salt mixture (McCollum's), 3%; in addition, they received semi-weekly, 5 cc. of cod-liver oil by pipette, and 35 mg. of ascorbic acid subcutaneously. Casein was prepared as follows: Milk powder was dissolved in 10 v. of water at about 80° C., precipitated with CH₃COOH at the same temperature and rapidly filtered on a vacuum funnel. Twice the precipitate was eluted in cold water at about 4°, in a slightly acid medium, and filtered. Then it was gradually dissolved in a solution of CO₂NaH at 40°, which later was filtered. Finally, a new precipitation was performed, the precipitate being again washed twice and most of the water being extracted by pressure. This diet was also partly deficient in B-complex factor, which fact was erroneously expected to facilitate the development of beriberi.

† Bervitine Rhone-Poulenc.

injections started acute attacks of dyspnea, sometimes producing the death of animals. Better results were obtained in 6 animals (Nos. 7, 8, 13, 14, 17, 30) treated by dissolving 5000 gammas of thiamin in drinking water daily.* The attacks of contracture completely disappeared in Nos. 13 and 14, the former appearing quite normal. The adolescent female (No. 8) began menstruating. Paralysis regressed in Nos. 7, 8 and 31, but it was not modified in No. 14. The animals, however, did not gain over or equal the weight previously lost. In short, a definite improvement was produced by thiamin, and at any rate, there was no aggravation, since probably most of these animals would have been dead by this time (November 1) had thiamin not been given. But the improvement was slow and did not seem to be complete.

The immediate cure of spastic phenomena was to be expected, as thiamin quickly suppressed opisthotonos and other spastic accidents in pigeons and other animals.¹²⁻¹⁴ The very slow rate of improvement of the paralysis was due to the intensity of nerve degeneration, since the length of treatment for paralysis in B₁ deficiency was found to be proportional to the number of degenerated axones in the pigeon sciatic nerve.^{13,14} Cowgill³ and Street *et al.*¹² had even observed cases of well-advanced paralyses which could not be cured at all. As for the inability of the animals to regain their previous weight when treated with thiamin, this suggested the possibility of another food deficiency affecting the growth, possibly a lack of riboflavin, although carrots and cabbage contain a fair amount of it, or, as suggested by Cowgill† a lack of B₆, which might also account for some of the cardiac symptoms, as in cases described by Thomas *et al.*¹⁵

Discussion. It is well known that, in lower animals, a B₁-free diet produced few or none of the clinical symptoms and nerve lesions characteristic of beriberi.⁴ In humans likewise, Williams *et al.*¹⁸ did not observe marked clinical symptoms on a diet very low in thiamin. These findings were in agreement with the absence of clinical and pathologic disturbances in our experimental monkeys given a diet without thiamin.

On the other hand, a diet *partially* deficient in B₁, when given to lower animals, caused numerous clinical symptoms^{13,14} and a marked nerve degeneration,¹² both suggestive of beriberi. In our cases of typical beriberi in the monkey, the thiamin content of the diet was estimated to be about one-half the minimal requirement.

On the basis of these observations, it seems reasonable to conclude that only when the deficiency of B₁ is partial does one obtain the clinical and pathologic picture considered as characteristic of beriberi.

* Five grams of glucose were added as suggested by Tonutti and Walraff.¹⁶ The increased thiamin requirement due to this amount of glucose was negligible in view of the quantity of thiamin given daily.

† Private communication.

Conclusions. 1. Twenty cases of a cardionervous disease observed in a *Macacus sylvanus* colony have been described. Clinical signs of polyneuritis and cardiac failure, autopsy findings of peripheral nerve degeneration and hydropericardium, and a diet partially deficient in vitamin B₁, indicate beriberi as the cause of this disease.

2. The adolescent (3-year-old) monkeys were the most susceptible to the deficiency, as all were stricken early. In younger animals the disease occurred later, was characterized by spastic phenomena and intense cardiac disturbances leading to an early death. Some older animals showed chronic and moderate symptoms which did not result in death.

3. Treatment of the animals with crystalline thiamin cured the animals, but only incompletely, thus suggesting that a prolonged deficiency determines permanent lesions. Menstruation was resumed after treatment with either wheat germ or, in 1 case, pure thiamin.

4. In experimental complete B₁ deficiency, death occurred before any outstanding clinical symptoms or marked histologic degeneration of the nerves set in. However, when 2 sub-beriberic adolescents were given the B₁-free diet, acute symptoms reminding one of fulminating beriberi were observed.

5. The observations, including the failure of a complete lack of thiamin to produce the symptoms or pathology of beriberi, suggest that only a partial thiamin deficiency results in beriberi.

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VITAMIN B₁ NOT HELPFUL IN PROTRACTED INSULIN SHOCK.

BY ESTHER SOMERFELD-ZISKIND, M.A., M.D.,

EUGENE ZISKIND, M.D.,

ASSISTANT CLINICAL PROFESSOR OF MEDICINE, UNIVERSITY OF SOUTHERN CALIFORNIA
SCHOOL OF MEDICINE,

LAVON DALTON,

AND

VIRGINIA BUCK,

LOS ANGELES, CALIF.

PROTRACTED insulin shock sometimes follows a regular session of insulin shock treatment for schizophrenia. Usually the patient is awake within 15 minutes after sugar solution is given by nasal tube. But, exceptionally, even with the aid of intravenous glucose, the patient is not awake in an hour, and it becomes evident that he is in a state of protracted shock. Regardless of the amount of sugar given, he will not awaken for several hours or days or not at all. Or he may gradually respond aphasically, being none the worse for the experience, or may show adverse neurologic signs for months afterward.

In almost every article or discussion on the alleviation of prolonged coma, the injection of thiamin chloride has been advocated. However, Frostig⁶ places no confidence in this remedial agent and recently Cleckley and Templeton² reported its inefficacy.

The routine of insulin shock treatment requires large amounts of carbohydrate, usually in the form of sugar solution, to awaken the patient. Abundant carbohydrate increases the thiamin requirement¹⁵ and a high carbohydrate diet is most effective in producing the symptoms of B₁ avitaminosis. In the avitaminotic animal, minced brain tissue has not so great a capacity to utilize oxygen as in the normal animal.¹⁶ On the addition of crystalline thiamin chloride to the test tube, avitaminotic brain tissue takes up increased oxygen, whereas the normal pigeon brain does not. Certain brain cells of the B₁-deficient pigeon have a lowered respiratory rate in the presence of dextrose, a condition remedied by the addition of thiamin chloride.¹³ The latter increases oxygen consumption only in the B₁-deficient man or animal, relatively enormous doses being without effect in normals.¹¹ According to Holmes,⁷ the taking up of oxygen by the gray matter is increased after the addition of dextrose and reduced during insulin. Damashek and Myerson² demonstrated in insulin shock a decrease in the use of oxygen in the brain and attributed the neurologic symptoms in hypoglycemia to this diminished oxygen content.

Chemical analysis of the minced brain of the avitaminotic pigeon reveals pyruvic acid and methyl glyoxal, both of which are absent in the normal. These abnormal metabolites disappear on the addition of thiamin chloride. After carbohydrate metabolism has been

disrupted by monoiodoacetic acid or hyperinsulinization, methylglyoxal and pyruvic acid can be demonstrated in muscle. The theory has crystallized¹² that vitamin B₁ functions as a coenzyme in the metabolism of carbohydrate, more specifically in the oxidative breakdown of pyruvic acid. The great similarity of convulsions induced by thiamin deficiency, methylglyoxal and insulin has been pointed out.

There are other parallels between hyperinsulinism and B₁ avitaminosis. It is said that idioacetic acid or insulin overdosage leads to elaboration of methylglyoxal or pyruvic acid in toxic concentration, and that the mustering of sufficient vitamin B₁ reserve will overcome the toxicity from insulin. Dioxycetone decreases insulin convulsions; pyruvic acid and methylglyoxal increase them.⁴

Demole¹ gave insulin shock to 39 rabbits with 1 unit of insulin per kilogram of body weight. Of these, 13 each got 4 injections subcutaneously of 500 units of thiamin chloride 2 hours preceding the insulin, while 16 rabbits got no vitamin B₁. Of the latter, 11 had convulsions, recuperating spontaneously; all comas lasted more than 7 hours, in all the blood sugar went below 50 mg. In the vitaminized rabbits, only 2 had convulsions, 1 recuperating spontaneously; all remained in coma less than 7 hours; 5 stayed above 50 mg. blood sugar and 8 under.

Freudenberg^{5a,b} has often been quoted as the authority for the use of thiamin chloride to relieve protracted insulin coma. He had some insulin shock patients who, 30 minutes after being tube-fed with 400 cc. of 50% glucose solution, were not awake and who for several consecutive days had to be aroused with 140 cc. of 33% fructose intravenously. When given 2.5 gm. thiamin chloride 20 to 30 minutes after the tube feeding, the same patients awoke quickly, so that intravenous sucrose was not necessary. Freudenberg averred that administration of vitamin B₁ would improve the hypoglycemia even before sugar was given.

Leitao¹⁰ induced shock in a patient with 50 units of insulin, reducing the blood sugar below 30. Three minutes after an ampoule of betaxin was given intravenously, the blood sugar was 39. Another patient was given shock with 60 units of insulin, the blood sugar many times being lower than 30. After 4 hours, shock was interrupted by intravenous injection of 3 ampoules of vitamin B₁. Two minutes after the injection, the blood sugar was 45 and 3 minutes later 53. The author was not explicit as to the intensity of the shock.

According to Akos,¹ vitamin B₁ prevents hyperactivity and convulsions during shock and protracted coma if the vitamin is injected 16 hours before the insulin. "The organism must have been previously saturated with the betaxin to be effective." In 2 of our patients, there did seem to be a lessening of hyperactivity when we gave 5 to 10 mg. of thiamin chloride intramuscularly 16 hours before the insulin daily, and no convulsions or prolonged comas occurred

TABLE 1.—EFFECT OF VITAMIN B₁ ON TIME OF AROUSAL FROM INSULIN SHOCK AFTER SUGAR-FEEDING IN 27 PSYCHOTIC PATIENTS.

Mode of administration.	Name of vitamin preparation.	Amount given.	Units of vitamin B ₁ .	No. of patients in group.	No. of observations.	Insulin dose in units.		No. of minutes of hypoglycemia before administration (plus vitamin B ₁ where later given).		No. of minutes to awaken.	
						Range.	Mean.	Range.	Mean.	Range.	Mean.
By mouth (in tube-feeding)	Galen B syrup	½ oz.	1,500	17	90	30-330	172	180-334	255	0-57	20
	Galen B tablet	½ tablet	1,500	7	38	55-190	144	165-307	262	4-40	11
	All cases given		1,500	17	128	30-330	164	180-334	259	0-57	13
		1 oz.	3,000	14	69	30-280	132	241-350	302	0-35	13
Subcutaneously	Galen B syrup	1 tablet	3,000	12	69	30-300	121	242-344	294	-1-42	12
	Galen B tablet		3,000	14	138	30-300	128	241-350	298	-1-42	12
	Thiamin chloride	1 cc.	3,000	13	73	25-240	122	221-345	288	-1-30	10.4
	Thiamin chloride	1 cc.	3,000	14	50	40-320	122	221-345	289	-1-43	12
Intravenously	All cases given		3,000†	14	123	25-320	122	221-345	288	-1-43	11
			3,000	15	261	25-320	125	231-350	293	-1-43	12
	Thiamin chloride	1 cc.	15,000	6	32	35-240	120	214-307	256	5-25	11
	All cases given vitamin B ₁			27	421	25-330	127	180-350	280	-1-57	12
	Controls		...	27	229	25-340	147	168-349	271	-2-185	13

* Orally.

† Parenterally.

Age Distribution: Range, 15-48 years; Mean, 29 years. Sex: 9 Males, 18 Females. Period of Study: October, 1938, to November, 1939.

in these 2 patients. In 1 of our cases, where 120 to 240 units of insulin was the shock dose, 100 mg. thiamin chloride daily may have decreased the hyperactivity during coma, but it did not eliminate it; in fact, we were forced to give the patient 3.5 gr. of sodium amytal during this stage, in addition to having an orderly with the patient to keep him from injuring himself by thrashing about. Cleckley and Templeton² reported prolonged coma in 1 patient who had previously been prepared with thiamin chloride.

Experiment. From October, 1938, through November, 1939, we tested the effect of vitamin B₁* on the arousal time of 27 insulin shock patients. During alternate periods, different patients were given no vitamin, so that at all times there was an equal number of controls and experimental subjects. The vitamin was tried by mouth, intravenously and intramuscularly, always just as we were ready to terminate the hypoglycemia by pouring the tube feeding, the tube being already in place. Our time of termination was 4 to 4½ hours after the insulin was administered, the patient having been unconscious in each case about 2 hours. From the accompanying table, it is evident that this use of vitamin B₁ made no statistically significant difference in the arousal time of insulin shock patients.

Comment. Of course there is a dearth of experimental evidence with regard to prolonged insulin coma, since each investigator fortunately has experienced only a few instances. Such shock situations come mostly after many shocks which were promptly reversible. There is more danger of protracted coma in the period of increasing sensitivity to insulin, in the first week or two, particularly if the dosage is increased by leaps and bounds or when hypoglycemia is permitted to run longer than 4 or 4½ hours. We know that in animals the long-protracted comas are not reversible.

Storage of thiamin is widespread in the body, the highest concentrations being in liver, kidney, heart and brain.¹⁷ The latter retains most of its thiamin in B₁ avitaminosis even at the expense of other tissues. Animals deprived of vitamin B show disturbances of carbohydrate metabolism similar to those of diabetes, that is, the tolerance for dextrose is diminished.⁹ "Severe degrees of diabetes are not observed but the level of blood sugar is elevated enough to provoke glycosuria when carbohydrate is administered to animals or men long deprived of vitamin B₁."¹⁴

In protracted insulin coma there is often hyperglycemia and fever, and it is useless in these cases to keep plying the patient with sugar when the brain cells are probably "in a histiotoxic condition, unable to utilize the sugar."⁸ Heavy decrease of blood chlorides may also lengthen the shock.⁸ "The great loss of chlorides through profuse sweating and increased production of gastric juice may explain these findings." In addition to salt feeding, Kant suggests pushing fluids in prolonged coma, as there is probably a disturbed water balance too.

* We are indebted to the Galen Company, Inc., Berkeley, Calif., for all of the vitamins used in our experiment.

We have given a full course of insulin comas to 80 patients, among whom there have been 4 prolonged comas. When the latter complication occurred, we continued treatment on small dosage of insulin after a rest period of a week, except that in one of our earliest cases we were afraid to take further chances. We have had no bad residua and no deaths. For termination of coma, it is our custom to tube-feed brown sugar dissolved in hot water. We weigh out 1 gm. of sugar for each unit of insulin. This has been sufficient, except in 1 case in which 1.5 gm. of sugar to each unit of insulin was required for prompt awakening. When less than 100 gm. of sugar is needed, we make the solution up to 500 cc.; when 100 to 150 gm. of sugar is used, we go up to 750 cc., and with 200 gm. of sugar or more, we give a liter of water. The sugar will absorb more quickly if boiled to a syrup, but this makes unnecessary work. For the last 8 months, we have added 4.5 gm. of sodium chloride to each tube-feeding, and have had no prolonged comas during this period.

Conclusion. According to the tests we have made with thiamin chloride during insulin shock, we would not expect it to be helpful in arousing a patient in protracted coma.

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STUDIES OF THE B VITAMINS IN THE HUMAN SUBJECT.

III. THE RESPONSE OF CHEILOSI TO VITAMIN THERAPY.

By THOMAS E. MACHELLA, M.D.,

INSTRUCTOR IN MEDICINE AND IN PHYSIOLOGY, UNIVERSITY OF PENNSYLVANIA MEDICAL SCHOOL; RESEARCH FELLOW, PHILADELPHIA GENERAL HOSPITAL, PHILADELPHIA, PA.

(From the Thompson Vitamin Clinic of the Philadelphia General Hospital and of the Kinsey-Thomas Foundation of the University of Pennsylvania Medical School.)

THE dependence of cheilosis on some nutritional disturbance was first suspected in 1911 when Stannus⁹ observed the development of the lesion in native Nyasaland prisoners who subsequently presented

a pellagraderm. Then, in 1915, Bahr,² described the lesion among indigenous prisoners in Ceylon, more especially those serving long sentences. He stated that the prison warden ascribed the sores at the angles of the mouth to the eating of salt fish and regarded, as a valuable remedy, the ingestion of half-cooked liver or liver soup. It was not until 1937, however, that Aykroyd and Krishman¹ noted that cheilosis in their experience coincided with a deficiency of some factor or factors of the vitamin B-complex. In view of the development of the lesion on a riboflavin deficient diet, Sebrell and Butler⁶ ascribed the lesion to a deficiency of that vitamin. Their observations were given support subsequently by the reports of Sydenstricker¹⁰ Oden,⁵ Spies⁸ and Jolliffe,³ who noted also a disappearance of the lesion following the administration of riboflavin.

The possibility, however, of a deficiency of other fractions of the B-complex being responsible, in part at least, for the development of cheilosis has been suggested by some of the reported data. Sydenstricker,¹⁰ for instance, noted a subsidence of the affection in a pellagrins while he was receiving only nicotinic acid. The seemingly beneficial effects of the nicotinic acid in this case, however, were ascribed to an adequate riboflavin content of the diet, especially since the lesion appeared in another of his pellagrins while he was being treated with nicotinic acid. Manson-Bahr⁴ also referred to some pellagrins in whom the cheilosis disappeared following the administration of nicotinic acid. Smith and Martin,⁷ furthermore, saw the lesion clear up in a patient on a diet deficient in riboflavin. They also observed its disappearance in 3 out of 4 patients when pyridoxine was administered; and in a fifth case, that did not respond to riboflavin or nicotinic acid, they observed complete healing only when liver extract was administered.

This paper summarizes a personal experience in the management of 17 cases of cheilosis. It includes some negative results after the administration of riboflavin alone and some favorable responses to pyridoxine and nicotinic acid; it also suggests, in some instances, the importance of an adequate ascorbic acid blood concentration.

Description of Cases and Method of Study. During the past year 17 patients with cheilosis have been observed at the Philadelphia General or the University of Pennsylvania Hospital. All of them had been on an inadequate diet, and 15 presented, in addition to the typical lesion on the lips, other manifestations of B-complex deficiency, including chiefly glossitis alone or glossitis associated with bilateral calf muscle tenderness; 16 had anorexia; 3 had clinical and laboratory evidence of scurvy.

In 12 of the 17 cases the cheilosis was confined to the angles of the mouth and in one of these the lesion was unilateral. In 4 others it involved, in addition, the vermilion of the lip; and in 3 of these, that had scurvy, each lip was completely affected, and in the other one (S.B., Table 1) the involvement was confined to a wide shallow

ulcer on the right half of the lower lip. A similar ulcer, without involvement of the angles of the mouth, was present on the lower lip of the final case, a pellagrin. Bleeding occurred only in those patients who had scurvy.

TABLE 1.—CASES THAT RESPONDED FAVORABLY TO PYRIDOXINE (B₆) THERAPY.

Case.	Age.	Sex and race.	False teeth.	Location of lesion on lips.	Duration of lesion prior to treatment (mos.).	Other manifestations of deficiency.	Amount of pyridoxine received (mg.).	Time in which healing occurred (days).	Primary diagnosis.
E.L.*	60	F. W.	+	Both angles	?	Glossitis, calf muscle tenderness	70 in 7 days (H)*	7	Acute cholecystitis
B.C.†	24	F. W.	0	Both angles	1	Glossitis	210 in 7 days	5	Alcoholism
F.R.	33	F. W.	+	Both angles	> 2	Glossitis, calf muscle tenderness	270 in 9 days (H)	7	Anorexia nervosa
I.H.	25	F. W.	+	Both angles	12	Reddening of oral mucous membranes	375 in 5 days	3	Diabetes mellitus
J.C.‡	52	M. W.	Uncompensated edentia	Both angles	1	0	375 in 5 days	5	Tabes dorsalis
M.R.	61	F. W.	+	Both angles	24	0	525 in 7 days	3	Diabetes mellitus
G.H.§	73	F. W.	+	Both angles	2=	Glossitis	600 in 20 days	Incomplete in 26 days	Osteoarthritis
T.D.	32	M. W.	0	Left angle	2	Glossitis	1050 in 7 days	7	Malnutrition
S.B.	63	F. W.	+	Both angles with ulcer on lower lip	‡ ?	Glossitis, peripheral neuritis	2100 in 14 days	14	Scleroderma, polyarteritis

* No response to previous course of nicotinic acid (3500 mg. over period of 9 days).

† Lesion recurred within 1 week after discontinuing administration of pyridoxine; permanent regression following second course of treatment and resumption of well-balanced diet.

‡ No response to previous course of riboflavin (92 mg. in 7 days).

§ Definite healing occurred during first 2 weeks of treatment, after which a course of riboflavin (75 mg. in 6 days) was substituted. The lesions became worse during period of riboflavin therapy but began to regress when pyridoxine was re-administered.

H = subcutaneous administration.

The cases may be divided into two groups: one, including 5 out-patients, kept on their usual diet, and the other, including 12 in-patients, in whom some change in the dietary habits occurred incident to their hospitalization. In the latter group, however, though an adequate diet was presented to each subject, he was allowed to choose what foods he wished. All supplementary vitamins except the one that was being tested in the case at the time

were withheld. That vitamin preparation, except when noted otherwise, was administered by mouth. Local applications to the lips were not permitted.

Results. A trial of pyridoxine (B₆) was made in 13 of the 17 cases. The cheilosis in 9 (Table 1) of these healed while they were receiving this vitamin. The lesion in 8 of them subsided within 3 to 14 days. In the ninth case (G.H.), in which the cheilosis was

TABLE 2.—CASES WHICH RESPONDED TO VITAMIN PREPARATIONS OTHER THAN PYRIDOXINE.

Case.	Age.	Sex and race.	False teeth.	Location of lesion on lips.	Duration of lesion prior to treatment (mos.).	Other manifestations of deficiency.	No response* (mg. in days).		Response* (mg. in days).	Primary diagnosis.
A.K.	19	F. W.	0	Both angles	3 (?)	Glossitis	195 in 7 B ₂	609 in 7 B ₆	N.A. 630 in 7	Rheumatoid arthritis
G.C.	50	M. W.	0	Lower lip (shallow ulcer)	½	Glossitis, dermatitis, diarrhea, calf muscle tenderness	N.A. 7800 in 7	Alcoholism, pellagra
M.J.	44	F. C.	0	Both angles and limbs	1	Glossitis, low blood ascorbic acid level	N.A. 7200 in 12	B ₂ 21 in 7	Ascorbic acid 1700 in 13	Sicklelema, lues (treated), scurvy
M.G.	55	F. W.	+	Both angles and limbs	2	Glossitis, low blood ascorbic acid level	B ₆ 1800 in 12	B ₂ 180 in 6	Ascorbic acid 1200 in 4	Unilateral sciatica, scurvy
E.S.	32	F. W.	0	Both angles and limbs	½	Low blood ascorbic acid level	Ascorbic acid 2600 in 10	Scurvy
J.M.	44	M. W.	+	Both angles	2	Glossitis	B ₆ 420 in 14	B ₂ 49 in 7	Brewer's yeast 7.5 gm. t.i.d. in 14 days	Multiple sclerosis
F.M.	69	F. W.	+	Both angles	?	Glossitis	B ₂ 70 in 7	B ₆ 70 in 7	...	Multiple sclerosis (?)
M.K.	69	M. W.	+	Both angles	12	Glossitis, calf tenderness	B ₆ 1050 in 7	B ₂ 64 in 14	Brewer's yeast 7.5 gm. t.i.d. in 14 days	Diabetes mellitus

* Nicotinic acid (N.A.); riboflavin (B₂); pyridoxine (B₆).

most severe, extensive and ulcerative, healing occurred only after 26 days; during this period riboflavin was substituted for the pyridoxine for 6 days, but during this time the ulcerations became worse, to regress on resumption of the pyridoxine therapy. The cheilosis in the other four patients (M.G., J.M., M.K., and F.M.; Table 2) treated with pyridoxine failed to improve during its administration. One of these (M.G.) received the vitamin subcutaneously

as well as orally. All of these also failed to respond to riboflavin. The course of their lesions will be described in another paragraph.

In 8 of the cases, including some that also received and responded favorably to pyridoxine, riboflavin therapy failed to produce any evidence of significant regression. Of these cases the lesion in 2 (J.C. and G.H.) responded favorably to pyridoxine and that of a third (A.K.), to nicotinic acid. The cheilosis in the fourth and fifth cases (J.M. and M.K.) failed to react satisfactorily to pyridoxine but disappeared while the patient was receiving brewers' yeast. That of the sixth case (F.M.) remained unhealed, even when pyridoxine was employed. In a seventh case (M.J.) a previous trial of nicotinic acid followed by a course of riboflavin was ineffective, and healing did not begin until a low blood ascorbic concentration was raised. In the eighth (M.G.), previous successive courses of pyridoxine and riboflavin administered orally as well as subcutaneously were ineffective, and the cheilosis did not begin to disappear until her scorbutic state was corrected by the administration of vitamin C.

Two of the 3 patients with scurvy have already been referred to; the third one (E.S., Table 2) was more markedly scorbutic. She had the typical manifestations, including a positive tourniquet test. Her blood ascorbic acid level was 0. Her diet consisted only of 16 to 21 bowls of milk and oatmeal daily for a period of 9 months. No manifestations of a B-complex deficiency were noted, but she had at each angle of the mouth a wide fissure which bled freely and the vermilion of her lips was dry, desquamating and oozing blood. The involvement of her lips cleared up entirely within 1 week after the administration of vitamin C.

One patient (A.K.) has already been mentioned as having responded favorably to nicotinic acid, after riboflavin and pyridoxine had been without effect, and another one (G.C.), an alcoholic pellagrin, did likewise. He had, as manifestations of a B-complex deficiency, anorexia, calf muscle tenderness, bilateral symmetrical dermatitis limited to the dorsum of the hands, diarrhea and mental incoherence, and, in addition, on his lower lip a shallow, wide crater resembling an epitheliomatous ulcer, except that there was no induration beneath it. The ulcer healed completely within 5 days after the administration of nicotinic acid.

Recurrence of the cheilotic lesion occurred in 2 of the patients (B.C. and F.R., Table 1). In one of these (B.C.) healing occurred after the daily administration of 30 mg. of pyridoxine for 5 days. Two days later the treatment was stopped, and after another week the lesion had recurred. Again, however, after the daily administration of 30 mg. for a week it subsided and has not reappeared. The other patient (F.R.), with anorexia nervosa, responded satisfactorily to pyridoxine administered subcutaneously for a week, but the lesion reappeared a week after the therapy was abandoned. The

vitamin was then administered orally with no improvement whatsoever; in fact, the lesion became more severe and pustular. It was then discovered that she had been picking at the angles of her mouth with her fingernails, and so perhaps tending to prevent healing.

Comment. That cheilosis frequently subsides during riboflavin therapy appears to be definitely established by several reports in the literature. In some of the cases (Sydenstricker;¹⁰ Oden⁵) the lesion recurs when the administration of riboflavin is discontinued. This may be interpreted to indicate either that a riboflavin deficiency is responsible for the cheilosis or that the administration of riboflavin, which is appetite-restoring in an individual deficient in this vitamin, is accompanied by the consumption of an increased quantity of food and this food contains some substance that brings about healing of the lesion. The latter possibility must always be taken into consideration in connection with the disappearance of a symptom or sign during the administration of a vitamin. At any rate in the present series 8 of the patients treated with riboflavin showed no improvement during its administration, and none of them had any of the other manifestations that characterize the syndrome of ariboflavinosis.

That the administration of pyridoxine also may be followed by a disappearance of the cheilotic lesion is evidenced by the report of Smith and Martin,⁷ who noted healing after treatment with this vitamin, and by the observations reported in this paper. That still other members of the B-complex may be responsible is suggested by the observation that in some patients the lesion heals only when the entire B-complex, in the form of liver extract or brewers' yeast, is being supplied.

That a deficiency of cevitamic acid may also be related to the development of cheilosis is suggested by my observations on 3 patients in whom a bleeding lip lesion did not improve until the scorbutic state was brought under control.

Conclusions. The observations herein reported, as well as those of other authors, indicate that cheilosis is not necessarily a manifestation of riboflavin deficiency alone. Healing of the lesion often does not occur when riboflavin only is administered and, on the other hand, it may respond favorably to the administration of pyridoxine and, in some instances, of nicotinic acid. Furthermore, when the lesion is hemorrhagic and is accompanied by generalized involvement of the lips, especially of the vermilion, it may improve only when a low blood ascorbic acid level is elevated.

I am indebted to the chiefs of the medical and dermatologic clinics of the University Hospital and to Drs. Russell S. Boles, Charles L. Brown, Henry D. Jump, Samuel A. Loewenberg, Howard W. Schaffer, and the late Robert G. Torrey of the Philadelphia General Hospital for allowing me to make use of their clinical material for this study.

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A POST-REPEAL STUDY OF 300 CHRONIC ALCOHOLICS.

BY JAMES V. LOWRY, M.D.,

ASSISTANT SURGEON, U. S. PUBLIC HEALTH SERVICE, BETHESDA, MD.,

AND

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, SCHOOL OF MEDICINE, UNIVERSITY OF COLORADO;
DIRECTOR, COLORADO PSYCHOPATHIC HOSPITAL, DENVER, COLO.

REPEAL of the 18th Amendment in 1933 was followed by an increase in the number of admissions for chronic alcoholism at the Colorado Psychopathic Hospital. The average for the 2 years, 1931-1932, was 44.5 admissions, and for the 6 years, 1934-1939,

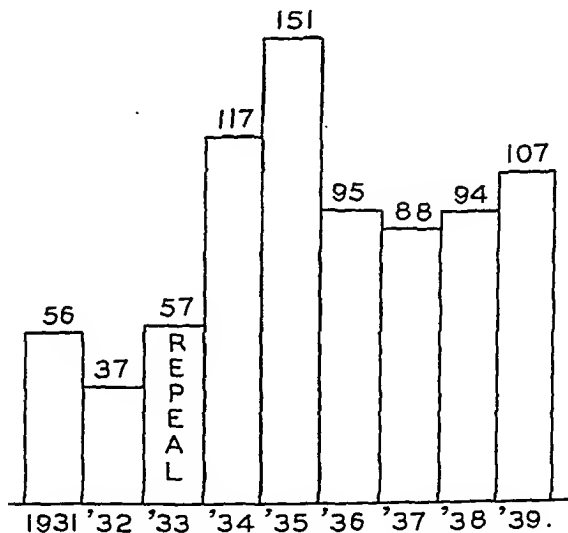


CHART 1.—Yearly admissions for alcoholism at the Colorado Psychopathic Hospital.

it was 107.7. Pollack's¹ figures for chronic alcoholism at the New York State Hospitals showed an average of 596 first admissions in 1931-1932, and an average of 850.4 for 1934-1938. During 1920-1923, a period of effective prohibition in New York, the average

number of first admissions for alcoholism at the same institutions was 204 per year.

The increase in the number of patients admitted for chronic alcoholism at this hospital prompted this investigation. Three hundred patients consecutively admitted during the years 1936-1939 were studied; 38 were readmitted patients. The data presented subsequently are based on this group. The continued use of alcohol was the direct cause of admission in each instance. Most of the patients entered the hospital because of coercion by relatives, and many of them resented being there. Only a few had more than a superficial desire to be rid of their habit. This was evident in their length of stay on first admission—57 (19%) left in less than a week—although an attempt was made not to admit any patient unless the responsible relative understood that a minimum of one month was necessary for any real attempt at therapy.

TABLE 1.—NUMBER OF DAYS IN HOSPITAL ON FIRST ADMISSION.

Days.	No. of patients.
1-7	57
8-14	56
15-21	55
22-28	60
29 or more	72
	<hr/> 300

These patients were quite frank, if not entirely accurate, in their statements regarding the amounts they drank. The preference for whisky was unanimous, but if the financial situation was difficult, a shift to wine occurred. Of these patients 107 (36.3%) were periodic drinkers who would have "sprees" of a week or two of continuous inebriety followed by periods of abstinence lasting from a few weeks to several months.

TABLE 2.—CONSUMPTION OF ALCOHOL.

<i>Whisky:</i>	
Minimum of $\frac{1}{2}$ pint daily	12
Minimum of 1 pint daily	45
Minimum of 1 quart daily	32
Determined by supply	85
Periodic debauches	107
<i>Wine:</i>	
About 1 gallon daily	19
	<hr/> 300

Ninety-eight (32.7%) of the patients were classified as psychotic on admission. The distribution as to type of psychosis is shown in Table 3. Twenty-two (22.4%) of the 98 psychotic patients, and 24 (11.9%) of the 202 patients without psychosis had a peripheral neuritis.

TABLE 3.—TYPE OF ALCOHOLIC PSYCHOSIS ON ADMISSION.

Organic deterioration	44
Delirium tremens	27
Acute hallucinosis	18
Korsakow's psychosis	9
	<hr/>
	98

If the consumption of alcohol was enough to produce frequent periods of intoxication or to interfere with the ability to earn a living, it was taken to be greater than social drinking and the individual regarded as a chronic alcoholic. Judged by these criteria, 170 (56.7%) were chronic alcoholics by the age of 30 (Table 4). The average age on first admission was 40 (Table 4). The duration of chronic alcoholism before first admission is shown in Table 5.

TABLE 4.—AGE INCIDENCE OF 300 ALCOHOLICS.

Age group.	At onset.	On first admission.
15-20	65	1
21-30	105	37
31-40	61	104
41-50	32	96
51 or over	16	62
Not given	21	
	<hr/>	<hr/>
	300	300

TABLE 5.—DURATION OF CHRONIC ALCOHOLISM PRIOR TO FIRST HOSPITALIZATION.

Less than one year	3
1-5 years	87
6-10 years	61
11-15 years	35
16-20 years	43
21 or more years	51
Not given	21
	<hr/>
	300

Information was obtained concerning the level of formal education attained by 273 of the patients; it varied from no school attendance to college graduation. Only 52 (19.1%) of the 273 failed to complete the eighth grade; 122 (44.7%) completed high school; and 41 (15%) attended college. The occupational records of the patients showed frequent changes of employment. Only 32 (10.7%) were able to support their dependents and themselves without receiving aid at intervals. Of the 48 women 36 (75%) were housewives. The distribution by occupation is shown in Table 6.

TABLE 6.—OCCUPATION.

Non-skilled laborers	61	Students	3
Skilled laborers	46	Prostitutes	2
"White collar" workers	39	Gamblers	2
Housewives	36	Bartender	1
Business men	30	Politician	1
Farmers	23	Not given	1
Salesmen	23		<hr/>
Lawyers, physicians, dentists	11		300
Firemen	6		

The sexual and marital adjustments of these patients were poor. A history of infidelity, impotence, or perversion was obtained in about 150 (50%) of the 300. At the time of admission syphilis was present in 24 (8%), and a history of gonorrhea was given by 49 (16.3%). One hundred and six (41.4%) of the 256 patients who had been married were either divorced or separated, and 12 patients had been divorced more than once (Table 7). Of the 135 patients who were still living with their wives, 48 (35.5%) gave domestic difficulties as the reason for drinking.

TABLE 7.—MARITAL STATUS.

Single	43	Widowed	15
Married	135	Not given	1
Divorced	81		<hr/>
Separated	25		300

Evidence of poor emotional adjustment was apparent in childhood in 95 (31.7%) of these patients. Sixty-two were "nervous," stubborn, pouty, shy, enuretic, or had night terrors. Twenty-six were over-dependent and carried this through to adult life.

TABLE 8.—CHILDHOOD PERSONALITY TRAITS.

Shy, pouty, "nervous," stubborn	39
Enuretic past the age of 7	18
Night terrors	5
Resented father	7
Unusual parental attachment	26
	<hr/>
	95

Ninety patients were associated with chronic alcoholic relatives in early life, and 20 others had suicide deaths or psychotic relatives in the immediate family.

TABLE 9.—FAMILY CHARACTERISTICS.

Patients with alcoholic fathers (48) or mothers (9)	57
Broken home due to separation of parents	35
Rigid, domineering parents	25
Suicide deaths in immediate family	11
Psychotic relatives in immediate family	9
"Nervous" parents	8
	<hr/>
	145

Improvement, either from a physical or psychiatric viewpoint or both, was made in 246 (82%). Despite this high percentage of improvement only 18 (6%) had a prognosis on discharge that was considered good, that is, no expectation of relapse. Twenty patients left before any treatment except emergency therapy could be instituted.

TABLE 10.—PROGNOSIS ON DISCHARGE.

Good (no relapse expected)	18
Guarded	137
Poor (relapse expected)	130
Very poor	7
Not given*	7
	<hr/>

299†

* Patients discharged within 24 hours.

† One patient died in the hospital.

An attempt was made to learn the type of adjustment made by these people after their discharge from the hospital. The shortest time from discharge to follow-up was 6 months, the longest 30 months, with a fairly even distribution between these two extremes. The method used for the follow-up was to contact the referring physician or the relative who was responsible for the patient at the time of hospitalization. There are many criticisms of such a method. No information could be obtained about 140 patients; 91 had returned to their pre-hospitalization status; and in so far as could be determined, 60 had not been intoxicated since leaving the hospital.

TABLE 11.—FOLLOW-UP STUDY.

Relapsed	91
No relapse	60
Dead	7
In prison	2
No information	140
	<hr/>
	300

Summary. 1. In the 6-year period following the repeal of prohibition (1934-1939), the average number of admissions per year for chronic alcoholism at the Colorado Psychopathic Hospital was 147% higher than the average for the 2 years preceding repeal (1931-1932).

2. One-third of the chronic alcoholics were psychotic on admission. The incidence of peripheral neuritis was 15.3%, with the incidence in the psychotic patients twice as great as in the non-psychotic group.

3. Chronic alcoholism began by the age of 30 in most of the patients, and the average age on first admission was 40.

4. Many patients were reared in family situations complicated by the presence of alcoholic or otherwise inadequate relatives, and showed evidence of poor emotional reactions in childhood.

5. Only 10% were able to make good adult economic and marital adjustments. Of the 256 patients who had been married 41% were either divorced or separated.

6. Most of the patients left the hospital before receiving adequate therapy. Only 6% were given a good prognosis at the time of discharge, although 82% were considered improved by hospitalization.

7. As far as could be determined, 20% of the 300 patients had not been intoxicated for a minimum of 6 months after leaving the hospital. Thirty per cent were known to have returned to their pre-hospitalization status of chronic alcoholism, and no information was obtained on about 47% of the patients.

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BOOK REVIEWS AND NOTICES

FOUNDATIONS OF NEUROPSYCHIATRY. By STANLEY COBB, A.B., M.D., Bullard Professor of Neuropathology, Harvard Medical School; Psychiatrist in Chief, Massachusetts General Hospital. Pp. 231. Second revised and enlarged edition of the work formerly known as A Preface to Nervous Disease. Baltimore: The Williams & Wilkins Company, 1941. Price, \$2.50.

THE anatomy, physiology and pathology of the nervous system represent only a means to an end for the majority of students and physicians, namely a way "to understand the simpler workings of the central nervous system" and the reasons for its abnormal reactions. As "only a few simple mechanisms of the nervous system are thoroughly understood," the author wisely decided to "mention only those anatomical structures the physiology of which is known and to discuss only physiological processes for which there is at least a fairly well substantiated anatomical correlation." The choice of the material is free from false respect for time-honored schemes as well as sensational novelties. Clinical requirements have determined the selection of, and ably illustrate, the anatomic and physiologic data discussed in this book. There is no timidity in raising the question of consciousness and unconsciousness or the body-mind problem. No philosophic treatise is given as solution but appropriately simplified considerations are offered to the reader. Obsolete antitheses such as "organic-functional diseases" and "physical-mental phenomena" are forcefully attacked and placed in correct perspective.

The author believes "that Sherrington's idea of integration gives a working hypothesis upon the basis of which one may be eventually able to explain the higher mental functions." He does not hesitate to state his personal opinion in such controversial questions as cortical localization *vs.* function of the brain as a whole.

The book opens with the discussion of structure and function of the autonomic nervous system and its importance for internal medicine as well as for neurology and psychiatry. The antagonistic mechanism of micturition is clearly exposed and the interaction of fear, tachycardia, increased blood pressure, goose-skin, etc., exhibited. The presentation of segmental and suprasegmental apparatus in the central nervous system includes the reflex mechanisms of spinal cord and brainstem, the functions of the cranial nerves, the respiratory and equilibratory systems, pathways and rôle of exteroceptive and proprioceptive stimuli and their integration in cerebellar and cerebral cortex.

The succeeding chapters deal with motor integration, locomotion, and functional localization in the cerebral cortex. The old and new motor system and the action of the basal ganglia in contrast to the cortex are stated and the various levels of posture and locomotion described. The confused anatomic nomenclature of the basal ganglia is clarified by the help of a table, and the meaning of such debatable designations as rigidity and spasticity is clearly outlined. The different function, *e. g.*, of area 6 or of the cerebellum, in man and laboratory animals below apes is correctly stressed. Consciousness is defined as "a function of the organism in action." Under the title of unconsciousness, on the other hand, the problem of syncope is debated and the rôle of hemodynamics, blood chemistry and blood oxygen content in it. This leads to the excellent chapter on

cerebral circulation. The principal reflex arcs are shown controlling the bloodflow to the brain, comprising the carotid and aortic bodies, the cardiac, arterial and venous, pressure and chemical receptors, the angiospastic and vasodilating action, and the intracerebral control of bloodflow, the metabolic exchange between blood and tissue in the capillaries, and the lesions caused by oxygen deprivation.

Special chapters are dedicated to the spinal fluid, the general and special pathology of the peripheral and central nervous system. Epilepsy is treated not as a disease but as a pathophysiologic phenomenon, characterized by dysrhythmic brain waves. Its importance as a Public Health problem is exemplified by the statement that 650,000 persons in the United States are assumed to suffer from periodic seizures.

The last chapter, giving an introduction into psychopathology, calls for a broader approach to this problem. "There are psychiatrists who state that neurology can contribute nothing to their field; there are psychoanalysts who are interested only in 'interpersonal relations' and know nothing of the brain; there are neurophysiologists who deny psychology and consider analysis a 'racket.' What is important . . . is better training for everyone in all four fields and more tolerance. . . ."

The book is informative and stimulating and is highly recommended to medical students and physicians as well as to all instructors of biology and psychology.

F. L.

TECHNIQUES OF CONCEPTION CONTROL. By ROBERT LATOU DICKINSON, M.D., Former President, American Gynecological Society, and WOODBRIDGE EDWARDS MORRIS, M.D., General Medical Director, Birth Control Federation of America. Pp. 56; 50 illustrations. Baltimore: The Williams & Wilkins Company, 1941. Price, 50c.

IN a world of rapid change both socially and economically, an increasing interest and demand on the part of Society is developing in the matter of controlling reproduction so that the timing of pregnancies may be planned. Under such conditions marriage can take place earlier, and family size can be regulated according to the ability of the parents to give their children an adequate start in life.

For the proper regulation of reproduction the medical profession needs to be acquainted with the various methods that are effective. This is important as a single method is not necessarily suitable for every individual. Dickinson and Morris have produced a manual describing the various methods now in use, which should be in the hands of every physician who desires to fulfill his obligation to the patient needing such help. The subject is fully covered and its value greatly enhanced by a series of 50 excellent illustrations.

D. M.

BRUCELOSIS (Undulant Fever). Clinical and Subclinical. By HAROLD J. HARRIS, M.D., Health Officer, Westport, N. Y.; Consulting Physician, St. Lawrence State Hospital; Attending Physician, Elizabethtown Community Hospital, etc. Foreword by WALTER M. SIMPSON, M.D., F.A.C.P., Director, Kettering Institute for Medical Research, Miami Valley Hospital, Dayton, Ohio. Pp. 286; 44 text illustrations and 12 in color. New York: Paul B. Hoeber, Inc., 1941. Price, \$5.50.

ONLY 17 years have passed since the first proven case of human brucellosis of bovine origin was reported. Yet the writings of a few observers, including the author of this volume, have aroused an increasing awareness on the part of physicians of the widespread prevalence of this disease, with the result that several thousands of cases have been recognized yearly during the past

decade. For the most part these have been examples of the more acute forms of the disease. But recent clinical experience shows that chronic brucellosis is even more common, and constitutes a major cause of chronic ill health. Since the available information on brucellosis is restricted almost wholly to journal articles, the publication of a monograph on the subject is timely. It is therefore all the more regrettable that the book is open to a number of serious criticisms. In his enthusiasm to present the manifold clinical aspects of chronic brucellosis, the author has fallen into the very error which he says he wishes to avoid; that of attributing to brucellosis, without adequate proof, certain symptoms and findings that happened to be encountered in patients with chronic brucellosis. Examples are: duodenal ulcer; glycosuria; borborygmus; hematuria; alveolar abscess in 75% of cases (one patient had 28 abscessed teeth, but cultures were negative); sinusitis (usually frontal, "a frequent finding" in patients with chronic brucellosis); thyrotoxicosis. The factor of a non-specific protein shock effect is at times underestimated, as in deprecating the value of intravenous typhoid therapy in acute brucellosis recently acquired; at times overlooked, as in attributing too great a diagnostic significance to the response to brucella vaccine treatment in doubtful cases. The discussion of the control of the disease in lower animals, especially the problems presented by the infection in range cattle and in other animals, is inadequate. While the literature has been sufficiently covered, there is failure at times critically to evaluate much that has been included. Nevertheless, the book contains a wealth of useful information. Particularly well done are the description and interpretation of the various diagnostic tests and the discussion of the use of brucella vaccine in the treatment of chronic brucellosis. R. K.

CLINICAL PELLAGRA. By SEALE HARRIS, M.D., Professor Emeritus of Medicine, University of Alabama, Birmingham, Assisted by SEALE HARRIS, JR., M.D., Formerly Assistant Professor of Medicine, Vanderbilt University, Birmingham, Ala. With a Foreword by E. V. McCOLLUM, PH.D., Sc.D., LL.D., Professor of Biochemistry, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore. Pp. 494; 66 illustrations and 16 tables. St. Louis: The C. V. Mosby Company, 1941. Price, \$7.00.

It is a decided advantage to have an adequate description of so important and widely distributed a disease as pellagra presented in a single ready reference volume. McCollum in his introduction to the work, calls attention to the thread of etiologic philosophy and reflective comment on which the author has strung both clinical observation and literature, and rightly estimates this as an attraction and asset of the work, though perhaps in these days a bit of a space-consuming luxury.

The text covers history and epidemiology (3 chapters); historical review of causal investigation and theory (6 chapters); etiology and pathology (5 chapters); clinical investigations (3 chapters); symptomatology, diagnosis and prognosis (8 chapters); prophylaxis (3 chapters); treatment (3 chapters); bibliography circa, 600 titles; index, 21 pages.

Obviously a book of this scope will contain much for the expert in the fields which pellagra invades through its varied symptomatology, cutaneous gastro-intestinal, neurologic. The author has succeeded in maintaining a central thesis without reducing his presentation to polemic or propaganda. The cause of pellagra, or better the complete causal mechanism of pellagra is still unknown, and is probably an interplay of predisposing and exciting causes. The former include alcohol, corn toxins, gastro-intestinal infections or infestations, carcinoma and other chronic gastro-intestinal diseases. The latter include avitaminosis—nicotinic acid deficiency especially; defi-

ciency of the "gastric intrinsic factor;" liver disease or inadequacy resulting in inability to store or utilize nicotinic acid; and sunlight (photosensitivity). Harris' suggestions for experimental studies indicate the emphasis he places on gastro-intestinal and liver malfunction, the importance of bacteriologic and mycologic studies of pellagrous diets and the metabolism of coproporphyrin in relation to nicotinic acid utilization and deficiency.

In the body of the text the clinical delineation and differentiation of the typical "3 D" (dermatitis, diarrhea, dementia) pellagra, and the various atypical or what one might call the parapellagra manifestations, is well handled. The emphasis on endemic character and national and world-wide distribution is still timely. Treatment is dealt with with the sure touch of experience and much interesting detail. The recommended dosage of nicotinic acid (100 mg. daily at one point) seems small. The interrelations of sprue, pernicious anemia and pellagra are constructively used in integrating the multiple causal concept to which the author gives his support.

The presswork is excellent, the photography fair (some badly focussed subjects), the color plate of the pellagrous tongue the best the Reviewer has seen, though too much reduced. A close-up showing the detail of the highly characteristic keratotic or steatotic "saddle" over nose and cheeks would be a useful inclusion in a future edition. The price of the work is too high considering its value to the large number of physicians who could and should use it.

J. S.

PHYSICAL MEDICINE. The Employment of Physical Agents for Diagnosis and Therapy. By FRANK H. KRUSEN, M.D., F.A.C.P., Associate Professor of Physical Medicine, the Mayo Foundation, University of Minnesota; Head of the Section on Physical Therapy, the Mayo Clinic, etc. Pp. 846; 351 illustrations. Philadelphia: W. B. Saunders Company, 1941. Price, \$10.00.

THIS work, as stated in the preface, "has been written with the purpose of presenting in one volume the modern concepts of the subject of physical medicine." The book fills a crying need because, to quote again the author, "Although there are excellent books available which deal with one or two branches of the subject, as well as good large reference works, there is, perhaps, no other book which covers the whole subject in a way that has been attempted herein."

The author has been successful in attaining his purpose. All the various disciplines of physical medicine are presented in this work in a well-balanced form in one single volume and discussed in an authoritative manner, the book showing throughout evidence of having been written by a master in his field. The text is based essentially on the author's original studies and clinical experience, but also includes a great number of observations taken from other well-selected sources. To these sources detailed reference is given at the end of each chapter. Throughout the text the various phases of the subject matter are critically analyzed and evaluated. Polemic topics are presented, discussed impartially, the author frequently expressing his own opinions. These opinions are amplified by numerous case reports, graphs, and statistical data. As stated in the preface, "Throughout the text, particular emphasis has been laid on the simple physical measures which are readily adaptable for general practice."

The subject is divided into 9 parts. The first deals with the history of physical therapy. The next 5 parts are devoted to a discussion of the various branches of physical therapy according to the particular agent employed, namely, thermotherapy, light therapy (a particularly informative part of the book), electrotherapy, hydrotherapy, and mechanotherapy. Part VII treats of the clinical aspects of physical medicine with emphasis laid on physical therapy of arthritis, the relation of physical therapy to

orthopedic surgery and to its management of backache. The remaining 2 parts deal with the teaching of physical medicine and with the hospital department of physical therapy. The index is complete.

The reading of this volume should be of much benefit not only for the physical therapist, but also for specialists in other fields of medicine, as well as for the general practitioner.

J. N.

MEDICAL MANUAL OF CHEMICAL WARFARE. (First American Edition; Reprinted by Permission of The Controller of his Britannic Majesty's Stationery Office.) Pp. 119; 1 figure and 10 plates. Brooklyn: Chemical Publishing Company, Inc., 1941. Price, \$2.50.

THE first American reprint of this British publication will be welcomed as a valuable text for physicians who, as civilians or as officers in the armed forces, may be required to handle the casualties resulting from chemical warfare. Chapter headings include: General description of war gases; the vesicant or "blister" gases; the lung irritant or choking gases; paralyzant gases; arseniuretted hydrogen poisoning; gases used primarily as harassing agents; dangerous gases not used for offensive purposes, but which may be encountered under war conditions; protection against gas and air raids; the recognition and first aid treatment of "gas casualties." There are appended a tabular summary of gases, their properties, methods of recognition and first-aid treatment; a description of the technique of administration of oxygen; and the "Atlas of Gas Poisoning": a 15-page reprint, with 10 illustrations, of a pamphlet first used in 1918 by the Medical Research Committee. The presentation is concise, correct and adequate for practical purposes. As set forth in the foreword, "It cannot be too strongly emphasized that a speedy recognition of the type of gas which has caused casualties is essential for rapid diagnosis and treatment: these desiderata can only be obtained by timely and thorough knowledge of chemical warfare substances, their characteristics, and their effects on the human body." This volume fully meets the issue.

R. K.

BIOLOGY OF THE LABORATORY MOUSE. By the Staff of The Roscoe B. Jackson Memorial Laboratory, CLARENCE C. LITTLE, Director, GEORGE D. SNELL, Editor, J. J. BITTNER, A. M. CLOUDMAN, E. FEKETE, W. E. HESTON, W. L. RUSSELL, G. W. WOOLLEY. With a Chapter on Infectious Diseases of Mice by J. H. DINGLE, Harvard Medical School. Pp. 497; 172 illustrations. Philadelphia: The Blakiston Company, 1941. Price, \$7.00.

To indicate the purpose of this book it is difficult to improve upon statements in the preface: "Of all the laboratory mammals, probably none has contributed more to the advancement of knowledge than the common mouse. . . . A result of this extensive use of the mouse is . . . a large body of information . . . so widely scattered that it is often a major undertaking for the research worker who wishes to use it to locate and gather the particular facts that he needs. Much of this information is assembled in this book. In a number of cases . . . important gaps in the literature . . . have been filled in by special research projects. . . . Because it deals with the mouse alone, this book presents a vertical cross-section of biological knowledge rather than the more usual horizontal cross-section."

The book contains the following chapters, prepared as indicated by various authors, which with one exception are members of the staff of the Jackson Laboratory: 1, The Early Embryology of the Mouse; 2, Repro-

duction; and 5, Gene and Chromosomes Mutations—G. D. SNELL; 3, Histology—ELIZABETH FEKETE; 4, Spontaneous Neoplasms in Mice—A. M. CLOUDMAN; 6, The Genetics of Spontaneous Tumor Formation; and 7, The Genetics of Tumor Transplantation—C. C. LITTLE; 8, Endocrine Secretion and Tumor Formation—G. W. WOOLLEY; 9, The Milk Influence in Tumor Formation; and 13, Care and Recording—J. J. BITTNER; 10, Inbred and Hybrid Animals and Their Value in Research—W. L. RUSSELL; 11, Parasites—W. E. HESTON; 12, Infectious Diseases of Mice—J. H. DINGLE.

The text is abundantly illustrated by drawings, photomicrographs and charts. An extensive bibliography is appended to each chapter. The index is entirely adequate. The editor and authors of the various chapters are to be congratulated. All who use the laboratory mouse must feel a distinct obligation to them.

H. R.

PLAY FOR CONVALESCENT CHILDREN IN HOSPITALS AND AT HOME. By ANNE MARIE SMITH (Staff Instructor), Leaders' Training School, Community Recreation Service, Chicago, Ill. Pp. 133. New York: A. S. Barnes & Co., 1941. Price, \$1.60.

THIS small book outlines the growth of organized play on the wards of the Children's Memorial Hospital in Chicago. It is, however, a good deal more than that. It is convincing evidence of the value of intelligently organized play as an essential part of the treatment of sick children and as such should be required reading for a great many doctors, nurses and hospital administrators.

There is a brief but good discussion of the types of play suitable to varying types of situations such as that of the general ward, isolated, chronically ill, and preoperative patient. The references to more detailed special works and the list of suitable and popular books for the library are very helpful.

S. L.

CONDITIONED REFLEXES AND PSYCHIATRY (Vol. 2 of Lectures on Conditioned Reflexes). By IVAN PETROVITCH PAVLOV, Late Director, Physiological Laboratories, Institute of Experimental Medicine and Academy of Sciences, Leningrad; Late Professor of Physiology, Military Medical Academy, Leningrad, etc. Translated and Edited by W. HORSLEY GANTT, M.D., B.Sc., Medical Director, Leningrad Unit American Relief Administration, 1922-23; Coworker in Pavlov's Laboratory, Institute of Experimental Medicine, 1925-29; Associate in Psychiatry and Director Pavlovian Laboratory, Johns Hopkins University. Vol. 1, with the collaboration of G. VOLBORTH, M.D., Former Assistant to Professor Pavlov at the Military Medical Academy; Professor of Physiology, University of Kharkov, and an Introduction by WALTER B. CANNON, M.D., S.D., George Higginson Professor of Physiology, Harvard University. Pp. Vol. 1, 414; Vol. 2, 199. Illustrations, Vol. 1, 9; Vol. 2, 7. New York: International Publishers, 1941. Price, Vol. 1, \$3.50; Vol. 2, \$4.00.

FOR those who have read "Conditioned Reflexes, An Investigation of the Physiological Activity of the Cerebral Cortex," the present volume suffers by comparison. The former book is a clear, systematic presentation of an important series of researches. It includes speculation of which the validity may at times be questioned, yet always supported by impressive experimental evidence.

"Conditioned Reflexes and Psychiatry" is a collection of lectures obviously never planned as a series. Since each was delivered to a different audience, the introductory résumé of earlier work, essential in presentation

from the platform, becomes tedious to the reader through recurrence. Too seldom has the translator deleted such material. He has preferred literal rendition to clarity and grace of style. The admirable introduction bears ample internal evidence that the choice was imposed solely by reverence for the author. It will be deprecated by the reader primarily concerned with the subject; yet appreciated for retaining the full flavor of the vivid personality of the great physiologist.

A more serious stricture is the almost complete absence of protocols, such as those which formed the backbone of the earlier book. Instead a relatively small number of experimental results are offered in support of a superstructure of theory which totters perilously far from its foundations.

G. McC.

OPTICAL ACTIVITY AND LIVING MATTER. (No. 2 of a series of Monographs on general physiology, edited by B. J. LUYET). By G. F. GAUSE, Professor of Experimental Biology, University of Moscow. Pp. 162; 18 illustrations. Normandy, Mo.: Biodynamica, 1941. Price, \$2.75.

AN editorial preface to this second in a series of monographs on general physiology ventures the suggestion that the optical activity of living material has not received attention among American biologists commensurate with its importance. The author has summarized adequately and completely the imposing literature on the structure and activity of living systems as related to the asymmetric configuration of their constituents. Fundamental questions concerning the origin, maintenance and inheritance of the so-called "natural" stereoisomers are presented concisely and speculated upon with a refreshing clarity obscured only infrequently by the author's apparent teleology.

The book is of value to biologists, physiologic chemists, and those engaged in fundamental medical research. Practicing physicians will find it readable, absorbing and informative; particularly will they appreciate the concise, restrained manner in which Professor Gause has presented the background of the recent controversy concerning the reported appearance of unnatural isomers in neoplasms. It is unfortunate that this definite contribution to our biologic literature will probably not receive the audience it deserves.

L. C.

ACCIDENTAL INJURIES. The Medico-Legal Aspects of Workmen's Compensation and Public Liability. By HENRY H. KESSLER, M.D., PH.D., F.A.C.S., Medical Director, New Jersey Rehabilitation Clinic; Formerly Medical Adviser, New Jersey Workmen's Compensation Bureau, etc. Pp. 803; 202 illustrations. Second Edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, \$10.00.

THIS book, which first appeared in 1931, is thoroughly revised in this edition. It is written from the point of view of a compensation administrator. In the first portion of the book, he has brought up to date the comparison of the various compensation laws as they relate to medical and hospital services. It is interesting to note that for every dollar paid for compensation and handled by stock companies, 42 cents goes to the carrier, 38 cents for cash compensation, and 20 cents for medical and hospital services.

Included in the book are many diagrams which serve to show at a glance the subject which the author wishes to emphasize. A very thorough section is given on examination and estimation of disability. A new chapter on the eye has been added by Dr. A. Rados.

This book, written largely by one man, is a statistical compilation and a

résumé of experience in the relation of accidental injuries to disease. It should prove extremely valuable to physicians doing compensation work, to insurance carriers, to compensation lawyers and to others interested in the relation of injury to disease.

L. F.

NEW BOOKS.

Functional Pathology. By LEOPOLD LICHTWITZ, M.D., Chief of the Medical Division of the Montefiore Hospital; Clinical Professor of Medicine, Columbia University. Pp. 567; 157 illustrations. New York: Grune & Stratton, Inc., 1941. Price, \$8.75.

The Retina. The Anatomy and the Histology of the Retina in Man, Ape, and Monkey, Including the Consideration of Visual Functions, the History of Physiological Optics, and the Histological Laboratory Technique. By S. L. POLYAK, M.D. A Fiftieth Anniversary Publication of The University of Chicago Press. Pp. 607; 100 illustrations (1 in color). Chicago: The University of Chicago Press, 1941. Price, \$10.00.

The Proceedings of The Charaka Club. Volume X. Post Multa Virtus Opere Laxare Solet. Pp. 260; illustrated. Baltimore: The Williams & Wilkins Company, 1941, for The Charaka Club. Price, \$5.00.

Eye Hazards in Industry. Extent, Cause and Means of Prevention. By LOUIS RESNICK. Pp. 321; 33 illustrations. New York: Columbia University Press, 1941, for National Society for the Prevention of Blindness. Price, \$3.50.

From Cretin to Genius. By DR. SERGE VORONOFF. Pp. 281. New York: Alliance Book Corporation, 1941. Price, \$2.75.

Nutritional Deficiencies. Diagnosis and Treatment. By JOHN B. YOU-MANS, A.B., M.S., M.D., Associate Professor of Medicine and Director of Post-Graduate Instruction, Vanderbilt University Medical School, Nashville. Assisted by E. WHITE PATTON, M.D. Pp. 385; 14 illustrations. Philadelphia: J. B. Lippincott Company, 1941. Price, \$5.00.

Better Nursing for America. By BEULAH AMIDON. (Public Affairs Pamphlet, No. 60, 1941.) Pp. 32; illustrated. New York: Public Affairs Committee, Inc., 1941. Price, 10c.

Sex Life in Babylonia. By EDWIN W. HIRSCH, M.D. (From the Urologic and Cutaneous Review, Sept., 1941.) Pp. 38. Chicago: Research Publications, 1941.

Sinus. By RUSSELL CLARK GROVE, M.D. Pp. 188; 16 illustrations. New York: Alfred A. Knopf, 1941. Price, \$2.00.

The Man Who Lived for Tomorrow. A Biography of William Hallock Park, M.D. Pp. 507; 1 illustration. New York: E. P. Dutton & Co., Inc., 1941. Price, \$3.75.

Pneumoconiosis (Silicosis). The Story of Dusty Lungs. A Preliminary Report. By LEWIS GREGORY COLE, M.D., Director of Silicotic Research, John B. Pierce Foundation, New York City, and WILLIAM GREGORY COLE, M.D., New York City. Pp. 21; illustrated. New York: John B. Pierce Foundation, 1940.

The Value of Health to a City. Two Lectures Delivered in 1873 by MAX VON PETTENKOEFER. Translated from the German, with an Introduction by HENRY E. SIGERIST. Pp. 52; 1 illustration. Baltimore: The Johns Hopkins Press, 1941. Price, \$1.00.

A reprint (Bull. Hist. Med., 10, 473, 1941) of two of Pettenkofer's lectures that were important in advancing the subjects of modern public health and medical economics.

Social Influences Affecting the Behavior of Young Children. By RUTH PEARSON KOSHUK. (Volume VI, No. 2, Serial No. 28.) *The Hearing of School Children.* A Statistical Study of Audiometric and Clinical Records. By ANTONIO CIOCCO, and CARROLL E. PALMER, Division of Public Health Methods, National Institute of Health, Bethesda, Md. (Volume VI, No. 3, Serial No. 29.) (Monographs of the Society for Research in Child Development.) No. 28, 71 pages; No. 29, Pp. 77; 14 figures and 40 tables. Washington, D. C.: Society for Research in Child Development, National Research Council. Price, \$1.00 each.

Xanthoma and Other Dyslipoidoses. By FRED D. WEIDMAN, M.D., L. NAPOLEON BOSTON, M.D., JOSEPH STOKES, JR., M.D., HOWARD W. SCHAFFER, M.D., WALTER FREEMAN, M.D., and F. W. SUNDERMAN, M.D., Philadelphia. Pp. 195; illustrated. Philadelphia: University of Pennsylvania Press for the Authors, 1941. Price, \$3.00.

The Medical Clinics of North America, Volume 25, No. 6, November, 1941. Military Medicine. Three Year Cumulative Index, Volumes 23, 24 and 25 (1939, 1940 and 1941). Pp. 417; 49 illustrations. Philadelphia: W. B. Saunders Company, 1941.

NEW EDITIONS.

Infant Nutrition. A Textbook of Infant Feeding for Students and Practitioners of Medicine. By WILLIAMS McKIM MARRIOTT, B.S., M.D., Late Professor of Pediatrics, Washington University School of Medicine; Physician in Chief, St. Louis Children's Hospital. Revised by P. C. JEANS, A.B., M.D., Professor of Pediatrics, College of Medicine, State University of Iowa, Iowa City. Pp. 475; 31 illustrations. Third Edition. St. Louis: The C. V. Mosby Company, 1941. Price, \$5.50.

Diseases of Women. By HARRY STURGEON CROSSEN, M.D., F.A.C.S., Professor Emeritus of Clinical Gynecology, Washington University School of Medicine; Gynecologist to the Barnes, St. Louis Maternity and St. Luke's Hospital, etc., and ROBERT JAMES CROSSEN, A.B., M.D., Assistant Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine; Assistant Gynecologist and Obstetrician to the Barnes and the St. Louis Maternity Hospitals, etc. Pp. 948; 1127 illustrations, many in color. Ninth Edition, entirely revised and reset. St. Louis: The C. V. Mosby Company, 1941. Price, \$12.50.

Medical Diseases of War. By SIR ARTHUR HURST, M.A., D.M. (OXON.), F.R.C.P., Lieutenant-Colonel, Late R.A.M.C.; Lecturer on Clinical Medicine, University of Oxford, and Consulting Physician to Guy's Hospital, etc. With the coöperation of H. W. BARBER, M.A., M.B. (CANTAB.), F.R.C.P., Physician-in-Charge of the Skin Department, Guy's Hospital, H. B. F. DIXON, M.C., M.D. (DUB.), D.T.M. AND H., F.R.C.P., Lieutenant-Colonel (temporary Colonel), R.A.M.C., F. A. KNOTT, M.D. (LOND.), M.R.C.P., Bacteriologist to Guy's Hospital, T. A. ROSS, M.D. (EDIN.), F.R.C.P., Late Medical Director of Cassel Hospital for Functional Nervous Disorders, and ARNOLD W. STOTT, M.A. (CANTAB.), F.R.C.P., Colonel, R.A.M.C., Late Consulting Physician to the British Expeditionary Force; Physician to Westminster Hospital. Pp. 427; 48 illustrations. Second Edition. Baltimore: The Williams & Wilkins Company, 1941. Price, \$5.50.

PROGRESS OF MEDICAL SCIENCE

MEDICINE.

UNDER THE CHARGE OF
JOHN H. MUSSER, M.D.,
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

GLOMERULONEPHRITIS.

Limitations. The investigations of Bright, Volhard and Fahr, Addis and many others have established the clinical and pathologic features that characterize the entity called variously glomerulonephritis, hemorrhagic nephritis or hemorrhagic Bright's disease. These features are too well known to require further elaboration. Although the picture as a whole is generally agreed upon, unanimity of opinion is not complete as to the precise criteria for diagnosis either pathologically or clinically. By means of special stains, Bell^{53a} has observed swelling of glomerular endothelium in kidneys from patients dying as a result of a great variety of diseases, and is led thus to conclude that there is no sharp histologic distinction between subclinical and clinical acute glomerulonephritis. From the clinical standpoint, Murphy and Rastetter⁵⁴ have stated that if the classic textbook picture of hematuria, hypertension and edema is regarded as essential for a diagnosis of acute nephritis, then many milder forms will pass unrecognized, and not until years later when chronic nephritis has set in will the true significance of the mild early episode become apparent. These authors followed the course of 150 patients diagnosed as having acute glomerulonephritis on the basis of albumin, red blood cells, casts and pus cells in the urine for one week or more, without necessarily having edema, azotemia or hypertension. The high incidence of unfavorable outcome (15.3 % died, 35.3 % became chronic) is evidence of the seriousness of the renal lesion in these patients. Some doubt has also been cast on the existence of the benign type of nephritis known as acute focal glomerulonephritis. According to Volhard and Fahr, this type of nephritis is a symptomless hematuria, occurring at the height of an acute infection, without edema, azotemia, hypertension or oliguria, and with a uniformly good prognosis. In a careful long-term study of more than 300 cases of nephritis in childhood, Payne and Illingworth⁶⁰ were unable to distinguish between focal and diffuse acute glomerulonephritis on the basis of the criteria mentioned.

Baehr,⁹ on the other hand, regards the viewpoint of Bell as a misinterpretation of a common postmortem finding analogous to the clinical error of diagnosing glomerulonephritis merely because of the presence of albumin and casts or of red blood cells in the urine. He believes: 1, that glomerulonephritis in its acute form is a sharply circumscribed entity; 2, that it is part of a disease of the body as a whole; 3, that its clinical manifestations can be related to characteristic pathologic phenomena in various parts of the body; and 4, that the disease has a specific etiology and pathogenesis.

As regards the relationship of nephrosis to nephritis, controversy continues between the two schools of thought.²⁸

Pathogenesis. The types of infection preceding the onset of acute glomerulonephritis in 976 cases collected from the literature³⁸ are as follows: sore throat, and tonsillitis, 32.1%; upper respiratory infection, 24.4%; scarlet fever, 6.4%; otitis and sinusitis, 5.7%; skin infections, 4.1%; pneumonia, 4%; rheumatic fever, 1.7%; miscellaneous, 10.3%; and infection unknown, 11.3%. Thus, infections of the upper respiratory tract including scarlet fever account for 69% of the cases.

Although other organisms such as the pneumococcus^{15,67} and *Streptococcus viridans*⁹ have been related to the etiology of acute glomerulonephritis, in most instances the hemolytic streptococcus has been incriminated. Not only have increased titers of antistreptolysin been found in serum,^{45a,48} but in one series^{45b} this organism has been recovered by culture in 90% of cases. Furthermore, there is evidence that the streptococcal infections preceding glomerulonephritis are usually of the "deep" type⁵⁵ in at least two-thirds of the cases,⁶⁸ as opposed to the superficial type of infection preceding rheumatic fever.

The exact manner in which the hemolytic streptococcus produces its effect on the kidney has not been established. The studies which may throw some light on this question have been reviewed by Longcope.^{45b} There is no evidence to show that the lesions are set up by direct infection of the kidneys, nor exclusively by the action of toxins. The interval of time between the onset of infection and the appearance of the first symptoms of nephritis varies from 3 to 28 days, the average falling on the tenth or eleventh day. This latent period suggested to Schick and to others a similarity to the incubation period of serum disease. Furthermore, following exacerbations of glomerulonephritis, this prodromal period is shortened to a few days,^{45b,69} calling to mind the accelerated reaction following a second injection of serum. Baehr⁹ has pointed out that, in subacute bacterial endocarditis due to the *Streptococcus viridans*, some immunologic reaction is necessary for the production of nephritis. Whereas, true diffuse nephritis is seldom seen in cases that have remained bacteremic until death, 33½% of those patients who have killed off their bacteria and entered the bacteria-free stage die as a result of typical diffuse glomerulonephritis.

In the past many investigators have attempted to reproduce glomerulonephritis in experimental animals by the use of streptococci or their products. The results have not been consistent and where nephritis has been produced it has not borne close resemblance to the disease in humans. The type of glomerulonephritis which at present is receiving most attention is that obtained by the injection of nephrotoxic sera. Introduced by Lindeman in 1900, this method has recently

been studied in the rabbit by Masugi and others,^{8,41a} in the rat,⁷¹ and in the dog,^{17,25} Organ-specific antiserum is prepared in another species (duck, hen, and so on) by injections of perfused and washed kidney tissue of the test species, and subsequently injected into the test animal. After a latent period which is short for the rat but longer for the rabbit and dog, renal injury becomes evident, and with repeated injections may progress fatally. Although it has been stated¹⁷ that nephrotoxic nephritis is a true antigen-antibody reaction and not due to antibodies to blood proteins, Kay^{41b} has presented evidence indicating that this simple explanation is insufficient and that an immune response to the donor's serum also plays a rôle. He found that inhibition of these antibodies by Roentgen irradiation prevented the nephritis, whereas prior injection of donor serum accelerated the reaction.

The studies mentioned above have all involved nephrotoxic sera produced in a heterologous species. Schwentker and Comploier,⁶⁵ employing the method of Burky¹⁹ for rendering homologous organs antigenic, have produced antikidney antibodies in rabbits by the injection of homologous kidney to which streptococcal toxin had been added. Having shown that homologous antikidney antibodies could be produced in the experimental animal, these investigators tested the sera of humans and found antibodies to rabbit kidney in 92% of patients with scarlet fever as against only 10% in normals. This suggests the possibility that, as a result of scarlet fever, patients may develop antibodies to their own kidneys. It is of interest at this time to recall that whereas full-blown glomerulonephritis is said to follow in less than 5% of cases of scarlet fever,³⁸ Lyttle^{47a} has demonstrated by the Addis technique^{6a} that many patients during recovery from scarlet fever show a transient but often significant increase in the excretion of albumin, casts, leukocytes and red blood cells in the urine.

The production of glomerulonephritis in rats by the subcutaneous injection of plasma, serum or their ultrafiltrates from patients with glomerulonephritis has been reported by Sehober,⁶⁵ and interpreted by him as demonstration of a toxic principle which is the cause of glomerulonephritis.

A consideration of certain biologic differences between glomerulonephritis and rheumatic fever has been presented by Seegal and Earle.⁶⁸ Their summary is as follows: 1, Although both diseases appear to be initiated by Group A hemolytic streptococcal infection, the geographic incidence of acute glomerulonephritis is similar for all latitudinal regions in North America, whereas the incidence of rheumatic fever is less frequent in the southern than in the northern latitudinal regions of North America. 2, Although twice as many males as females contract glomerulonephritis, this sex variation is not apparent in rheumatic fever. 3, The preceding clinical infection in acute glomerulonephritis is a "deep" hemolytic streptococcal infection in at least two-thirds of the cases, in contrast to the usual superficial pharyngitis preceding the onset of rheumatic fever. 4, There is a distinct shortening of the latent period following infection in the exacerbations of chronic nephritis, as compared with that in acute glomerulonephritis. This shortening of the latent period in exacerbation or relapse is absent in rheumatic fever. 5, Relapse, while a rarity following the healed state of acute glomerulonephritis, is a common if not regular occurrence following the rheumatic episode.

Pathologic Anatomy. Dissatisfied with the two-dimensional picture of the pathologic anatomy of chronic Bright's disease as revealed in histologic sections, Oliver has undertaken a study in three dimensions by the methods of: 1, micro-dissection, and 2, the construction of models from serial sections. The results of his long and fruitful labors are published in a beautifully illustrated monograph.⁵⁸ There appears to be a striking similarity in the architecture of all forms of contracted kidneys no matter what combination of initial processes has produced the ultimate deformity. The alterations in structure involve the nephron, the vascular system and the interstitial tissue. As regards the nephron, two forms are predominant, the hypertrophic and the atrophic, although a single nephron may show either of these processes in different areas along its length. The hypertrophic nephron is characterized by marked hypertrophy and hyperplasia of the proximal convolution, especially in its terminal segment. The increase in relative volume may become as high as 10 times the normal. The glomeruli of such tubules may be decreased in size or, indeed, absent, as in the nephrons of the aglomerular kidneys of certain fish. Even in these aglomerular tubules, the cells retain the morphology of functioning cells, and differ greatly from the flattened cells of tubules that are passively dilated as a result of obstruction distally. The author is extremely cautious in interpreting the significance of these hypertrophied proximal convolutions, but increased function seems likely. The structure of the atrophic nephron is less complex, there being general reduction in size of all parts. In addition to aglomerular tubules, atubular glomeruli are found, and there may be interruptions of the continuity of the nephron at other points along its course, with apparent survival of the segments. The distal convolution as a result of its functional and structural characteristics is the site of early occlusion with debris and, by this stoppage, it may become the point of origin of a distortion of the entire nephron.

The transformation of the architecture of the arterial tree is equally profound. The well-known changes in the afferent arterioles and the glomerular capillaries are evident, but there is an alteration of even greater significance involving Ludwig's vessel. This vessel, arising from the afferent arteriole, serves to shunt blood directly to the peritubular capillary plexus, avoiding passage through the glomerulus. Whereas in the normal kidney Ludwig's vessels are few in number, they are found with significant frequency in all forms of terminal Bright's disease. The demonstration of this compensatory blood supply to the tubules in kidneys in which the glomerular capillary bed has been blocked appears to solve a problem that has long taxed the ingenuity of pathologists.

Judging from the architectural pattern of the contracted kidney of Bright's disease, Oliver cannot escape the conclusion that there must have occurred a shift in the normally predominating glomerular functional balance towards a condition of increased tubular elimination. The structural evidence which compels this conclusion is dependent on the demonstration of: 1, aglomerular tubules; 2, marked hypertrophy and hyperplasia of proximal convolutions; and 3, a shift in the circulation of the blood from a primarily glomerular distribution to a direct tubular supply.

Bell has recorded his findings in 110 cases of acute nephritis^{13a} and in 181 cases of subacute and chronic glomerulonephritis, including lipoid nephrosis.^{13b} He objects to the usual tendency of writers to discuss acute nephritis as a clinical entity assuming the underlying pathologic process in the entire group to vary only in intensity and not in character. He divides acute glomerulonephritis into 7 types and 2 of these into additional subtypes. The initial glomerular lesion in the most common type, which he calls acute proliferative glomerulonephritis, is described as consisting of an increase of endothelial cells and a splitting and fragmentation of the central capillary basement membranes in the interior of the lobules, the latter being demonstrated by means of special stains. Azotemic glomerulonephritis is characterized by obstruction of the glomerular capillaries whereas in hydropic glomerulonephritis (lipoid nephrosis) the capillary walls are injured but the lumens remain open. This last type of lesion is considered characteristic of membranous glomerulitis.

Physiology of the Kidney. A somewhat abbreviated summary of the current concept of the physiology of the kidney as contained in the writings of Smith,⁷⁴ Richards⁶¹ and Hayman³⁷ seems in order at this point. The beginning of urine formation in man "consists in the separation of the protein-free filtrate of plasma by a purely physical process of filtration, the energy being derived from the heart. As this filtrate flows down the tubule, it is elaborated by the active reabsorption of water, glucose, chloride, sodium and other substances, by the diffusion of a fraction of such waste products as urea and uric acid back from lumen to blood as a result of the concentration gradient established by the reabsorption of water."³⁷ In addition, such foreign substances as phenol red (phenolsulphonephthalein), Hippuran and Diodrast are secreted by the tubule cells, as is creatinine under certain circumstances, and presumably ammonia and hippuric acid. In amphibia, the reabsorption of sodium chloride appears to be a definite function of the distal convoluted tubule, whereas glucose is reabsorbed almost entirely by the proximal tubule. Although some reabsorption of water occurs throughout the tubule, evidence indicates that it is maximal in the thin segment.⁷⁴

Inulin, a polysaccharide of high molecular weight, is eliminated entirely by glomerular filtration and is neither excreted nor reabsorbed by the tubules.⁷⁴ Consequently, its rate of excretion divided by the plasma concentration will be equal to the volume of the glomerular filtrate. Measured in this way, the average rate of glomerular filtration in the ideal man (1.73 sq. meters) is about 120 cc. per minute.⁷⁴ The filtration rate in normal man is essentially constant, and regulation of water excretion is effected primarily by regulation of the fraction of water reabsorbed by the tubules.⁷⁴ When creatinine is determined by newer analytic methods, the endogenous creatinine clearance is found to be equal to the inulin clearance and its use as a measure of glomerular filtration is advocated.⁷⁷ Simultaneous determination of the clearance of inulin and some test substance will enable one to calculate the degree of reabsorption or excretion of the test substance by the tubules. Thus the urea clearance is less than the creatinine clearance, indicating that urea reenters the blood from the tubule; on the other hand, the clearances of exogenous creatinine, phenol red, Hippuran and Diodrast are

greater, indicating that these substances must in part at least be excreted by the tubules.⁷⁴ Extensive studies based on this principle have been made in humans by Smith.⁷⁴ Other investigations have shown that the process of tubular excretion of certain substances is limited by the circumstance that a given mass of renal tissue can transport from blood to urine only a fixed, maximal quantity of a particular solute per unit time. The measurement of excretion for any one substance constitutes therefore a measurement of what may be called the "tubular excretory mass" of the kidneys.⁷⁵ The maximal rate of excretion is different for each substance. The highest yet obtained is that of Diodrast, and consequently, the Diodrast clearance may be used to express the minimal renal plasma flow, or by calculation the minimal renal whole bloodflow, which has been found in man to average 1300 cc. per minute.⁷⁵ By the use of these methods, it has been determined that the renal bloodflow is controlled predominantly by the efferent glomerular arterioles, these arterioles being normally partially constricted. Since, with efferent control, an increase or decrease in renal bloodflow is accompanied by an inverse change in filtration pressure, the filtration rate tends to be independent of the renal bloodflow.²³

Information obtained by the above methods in the study of the diseased kidney will prove valid only if the difference in function between the normal and the diseased organ is quantitative and not qualitative. That this cannot be tacitly assumed is implied by the anatomic studies of Oliver already described,⁵⁷ and by his demonstration of the altered handling of the dye trypan blue by the tubular cells of the kidney in naturally occurring canine nephritis.⁵⁸

Kidney Function Tests. The tests of renal function that continue to prove of practical usefulness are the tests of urinary concentration, phenolsulphonaphthalein excretion and urea clearance,^{11,79} less widely used is the quantitative study of the urinary sediment by the method of Addis.^{1a} The techniques of these procedures can be found in standard texts and need not be detailed here.

Other tests have been recently recommended, such as the orthotolidine test for hematuria^{10,29} and a test of the concentrating power of the kidney which obviates the necessity of a period of water deprivation by the use of pituitrin.⁷⁶ For determination of the rate of glomerular filtration an adaptation of the inulin clearance suitable for clinical use has been advanced^{4,52} as has also the endogenous creatinine clearance test, using improved methods for the analysis of creatinine.⁷⁷ Since the product of the plasma creatinine times the glomerular filtration rate is found to be relatively constant, a simple method for estimation of the glomerular filtration rate is suggested, that is, by dividing 86 by the plasma creatinine concentration.⁷⁷ Others consider the level of the plasma creatinine alone to be a sensitive index of kidney function.⁶

Pathologic Physiology of Glomerulonephritis. Recent additions to our knowledge of the pathologic physiology of glomerulonephritis have been obtained chiefly as a result of the application of new methods to the study of old problems, although, as might be expected, new problems have been unearthed in so doing.

The investigations of Burch¹⁸ explain why edema may appear first in the eyelids when there is a cause for generalized edema such as glomerulonephritis, and why it should accumulate during sleep. Whereas the

subcutaneous tissue pressure in the lower eyelid is approximately the same as that of the volar surface of the forearm the skin distensibility of the eyelid is much greater, and the subcutaneous tissues can accommodate a much greater volume of injected fluid for the same rise in tissue pressure. Direct studies indicate that linear rate of lymph flow in the eyelid is decreased by assuming the recumbent position and by lack of blinking, thus explaining the appearance during sleep and the disappearance on waking and rising. Also, the venous pressure in the eyelid is greater in the recumbent position than in the erect. Experiments in dogs suggest that the lower lid serves as a reservoir to take care of any increase in volume of interstitial fluid within the entire orbit.

The presence of an antidiuretic factor detectable by rat bio-assays in the urine of patients with acute nephritis, the nephritic syndrome, and other types of edema has been reported.⁶³ In some cases this factor was found to be absent after recovery from edema.

Hypertension in acute glomerulonephritis has been attributed chiefly to vasospasm following calorimetric studies of bloodflow during and after the hypertensive phase.⁷ The relation of the hypertension of glomerulonephritis to the number of patent glomeruli has been investigated.³⁹ When less than 700,000 glomeruli per kidney are patent (normal 1,250,000), the systolic blood pressure is invariably above 150 mm. Hg. Below this critical level, no correlation is evident.

Although it is often stated that the specific gravity of the urine tends to be high in acute glomerulonephritis, a special study of this point indicates that the capacity of the kidney to concentrate urine may be definitely impaired.³⁴

Determinations of the blood volume by the Gibson-Evans method in Bright's disease³⁵ reveal that plasma volume tends to vary directly with the serum albumin concentration and blood non-protein nitrogen level, and indirectly with the degree of anemia present. The total blood volume is below normal in all stages of the disease. When congestive heart failure occurs in chronic nephritis the levels of plasma and total blood volume are above average levels for comparable situations without heart failure.

There seems to be convincing evidence that in the nephrotic state protein in the plasma albumin fraction is altered; this has been demonstrated by a quantitative precipitin method³⁰ and by electrophoretic analysis.⁴⁶ Similar alteration in urinary albumin has been observed.⁴⁶ The significance of the albumin-globulin ratio of serum in the light of newer knowledge of the serum-protein complex has been considered in a recent report.⁵¹

Farr has summarized his many contributions to the understanding of protein metabolism in the nephrotic child.²⁴ The minimum nitrogen requirement necessary to insure positive nitrogen balance has been found to be 2.5 gm. of protein per kilo ideal body weight, nitrogen assimilation reaching a maximum at 3.5 gm. Dietary protein at the level 2.5 to 3.5 gm. per kilo ideal body weight over periods up to 6 years produced no deleterious effects on kidney function. Although feeding an optimal protein diet might be followed by positive nitrogen balance and freedom from edema, rise in plasma-protein concentration was not regularly produced. A period of negative nitrogen balance even on optimal diets was observed to precede acute clinical episodes termed

"nephrotic crises" with or without demonstrable infection such as pneumococci bacteriemia or peritonitis. Since transfusion therapy failed to alter the outcome, study of other factors in nitrogen metabolism was undertaken. For the first time it was demonstrated that the nephrotic patient exhibited a persistent hypo-amino-acidemia, with acute hypo-amino-acidemic crises accompanied by severe clinical manifestations when the level of plasma amino-acid nitrogen fell below the critical level of 2.5 mg. per 100 cc. A sharp rise attended clinical recovery. Amino-acid therapy by means of casein hydrolysate injected intravenously up to 2.25 gm. amino-acids per kilo ideal body weight per day did not influence the chronic hypo-amino-acidemia nor the hypo-proteinemia in spite of the fact that the casein hydrolysate was not excreted in the urine but was retained and utilized and was capable of replacing up to 57% of dietary protein nitrogen. In the crises of acute hypo-amino-acidemia, on the other hand, casein hydrolysate was of great clinical benefit and by this mode of treatment alone, without serotherapy or chemotherapy, mortality was reduced from the previous figure of 66% to zero in 11 cases of pneumococcal bacteriemia.

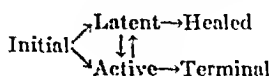
Studies of the mineral metabolism in chronic nephritis¹² have re-emphasized the possible harmful effect of diets high in sodium in promoting retention of fluid and elevation of blood pressure. The acid ions, phosphate and sulphate, whereas they promote diuresis and lowering of blood pressure, may lead to acidosis and an aggravation of the renal state, and are to be avoided in the terminal stages of nephritis.

The possibility that the azotemia of renal insufficiency might be due to normal or increased reabsorption by the tubules in the presence of decreased glomerular filtration has been denied as a result of experiments in which the urea clearance was studied simultaneously with the inulin or endogenous creatinine clearance.^{5,22,77}

Harrison and Mason³⁶ have reviewed the pathogenesis of the uremic syndrome. The various theories which have attempted to explain the manifold symptoms of uremia on the basis of some single toxic compound are not supported by adequate proof. The etiology is undoubtedly multiple. A known and definite rôle in the pathogenesis of uremia can be ascribed to a few substances. Calcium ion deficiency as a result of the retention of products forming un-ionized calcium salts is concerned in the initiation of motor irritative phenomena; phenol derivatives are related to the stuporous state; accumulations of organic and inorganic acids, as well as loss of base, play a rôle in the production of respiratory disturbance; depletion of chloride and of water increases the catabolism of protein and at the same time impairs further the ability of the body to excrete the resulting metabolites. There is strong evidence that other substances are also of pathogenetic significance. Guanidine-like compounds occur in excess in the blood and seem to play a rôle in the production both of motor irritative phenomena and of gastro-intestinal disturbances. Urea accumulation may be harmful either by initiating excessive fermentation in the alimentary tract, or by interfering with the processes of detoxification. As an index of uremia, a high xanthoproteic reaction of the blood and a high indican content are considered more valuable than the level of the blood-urea nitrogen.⁴²

Clinical Aspects. As stated by Longcope^{45b}, "a knowledge of the natural history of any disease is best obtained by observing the process from its

onset through the subsequent phases of its activity to its termination in recovery or in death. This method is a difficult one to pursue in a condition such as nephritis . . . which may last for many years." Certainly in no other disease is an understanding of the natural history of greater importance than in glomerulonephritis, with its tendency towards explosive or insidious onset, prolonged latency or chronic activity, and eventual healing or fatal termination. Of great aid in portraying this picture is the familiar diagram of Addis^{1b} or its modifications:



Acute glomerulonephritis may occur at any age but is more common in childhood than in adult life. The ratio of males to females is 2 to 1.⁶⁸ Rarely glomerulonephritis may appear in several members of one family.⁶² In Longcope's series^{45b} of 141 patients, chiefly adult, the disease commenced with the typical acute onset in 87.5 % and insidiously in 12.5 %.

In nephritis of acute onset, the predominance of one or another finding justifies the division into syndromes⁵⁴ as follows: *a*, urinary syndrome; *b*, hypertension; *c*, edema; *d*, nitrogen retention; and *e*, true uremia. The incidence of certain manifestations in two series^{38,54} respectively is: gross hematuria, 40 %, 32 %; edema, 58 %, 57 %; nitrogen retention, 43 %, 44 %; and uremia, 7 %, 7 %.

The hypertensive syndrome might well be called the cardiovascular syndrome, for many recent studies^{38,50,54,80} have emphasized the importance of cardiac insufficiency in acute nephritis. It is not necessarily related to arterial hypertension and may be recognized by dyspnea, pulmonary congestion, cardiac enlargement, gallop rhythm, elevation of venous pressure, slowing of the rate of circulation, enlargement of the Roentgen shadow of the heart and changes in the electrocardiogram. Circulatory insufficiency has been noted in 53 of 59 severe and in 12 of 35 mild cases of acute glomerulonephritis.⁸⁰ The electrocardiographic findings, summarized by Williams⁸¹ from 15 personal cases and 70 cases from the literature, consist chiefly in lowering or inversion of *T* waves, prolongation of the *P-R* interval and slurring of *QRS*. No correlation could be established between the occurrence of these changes and the signs of cardiac or renal insufficiency.⁸¹ The myocardial involvement in acute nephritis is considered by some⁸⁰ to be an expression of the widespread capillary damage occurring in this disease.

The characteristics of glomerulonephritis of insidious onset, without known antecedent infection, have been presented by Longcope.^{45b} Admitting that this type might quite possibly represent simply the active stage in the progress of glomerulonephritis of unrecognized onset, on the other hand, there would seem to be certain differences which distinguish this from the ordinary type, namely, a higher rate of unfortunate outcome, a lower incidence of skin reactions to streptococcal filtrates, and a lower incidence of elevated antistreptolysin titers.^{45b}

An important feature of glomerulonephritis is the tendency towards exacerbations of the disease, usually marked by an abrupt increase in hematuria. As emphasized in a recent study⁶⁹ such exacerbations are almost invariably preceded by some infection, usually with Group A streptococci. Curiously, in this study, reduction of renal function in such flare-ups was not invariable and seldom permanent.

Following the acute phase of glomerulonephritis latency or chronic activity may persist for years and careful study of the urine, blood pressure and kidney function at frequent intervals over long periods of time may be necessary to determine whether healing or activity is occurring, especially in those cases where such decision is not made obvious by progression into the terminal stage.

Prognosis. Collected statistics^{38,47b} indicate that the mortality rate of acute glomerulonephritis is fairly uniform in all series and averages 5% to 9%. There is no such uniformity of statistics as regards the eventual outcome beyond this stage, except for general accord in the better prognosis in childhood. Longcope^{45b} estimates the recovery rate for children to be 60% to 75%, and for adults 40% to 60%. The final classification as to outcome in any series depends greatly on the length of time followed and the completeness of the examination. In 495 cases collected from 7 reports³⁸ (followed 6 months to 14 years) the percentage of those said to be cured was 43% to 85%, latent 17% to 32%, and chronic 4% to 42%.

What are the factors that determine the prognosis in an individual case? Addis has stated that in this disease the end is determined by the beginning.^{1c} Yet the severity of the acute phase is apparently not of importance, except that where a definite infection is known to precede the onset of nephritis the prognosis is better.^{45b} The type of infection may have some bearing since it has been shown that healing of the renal lesion occurs in 90% of cases in which the preceding infection has involved the skin.²⁷ As stressed by Addis^{1b} and others^{38,60} of great importance in forecasting an unfavorable termination is the failure of healing to become apparent within 1 year. The persistence of foci of infection is considered by some^{45b,47b} to play a rôle in the progression of the renal lesion, and in support of this contention might be brought forward the relatively better prognosis where nephritis has followed infections of the skin, since the latter can nearly always be eradicated. In refutation of those who would remove all infected foci is the study of Illingworth⁴⁰ who failed to find early or late beneficial effects of tonsillectomy in 119 children subjected to this procedure during the acute phase of the disease. As has already been mentioned, exacerbations of glomerulonephritis are reported to produce only transient decrease in renal function in most cases. Thus, there is at present no final answer to this most important question of the factors concerned in the ultimate prognosis of glomerulonephritis.

Once complete healing of the renal lesion has been accomplished, it is most unusual for acute nephritis to recur, even following streptococcal infections.⁴⁴

Treatment. As regards prophylaxis, although the most frequent illness antecedent to nephritis is infection of the upper respiratory tract, and especially tonsillitis, it has been shown statistically, that tonsillectomy cannot be relied upon to prevent glomerulonephritis, and indeed it may even precipitate the development of this lesion.⁴⁰ It is possible that the widespread use of the sulfonamide drugs will reduce the duration, the severity, the number of complications and perhaps the incidence of hemolytic streptococcal infections, and in so doing reduce the incidence of acute glomerulonephritis.

A discussion of the treatment of the disease itself should properly

begin with a consideration of the question as to whether or not anything can be done to alter the course of the renal lesion once it has become established. Some of the factors concerned in this problem have already been discussed under the heading of "Prognosis." Regarding removal of foci of infection, little is to be gained by adopting the hopeless attitude, and it would seem wise to follow the recommendations of those who believe that persistence of infection spells progression of nephritis. Investigation of the value of the sulfonamide drugs is in progress.^{45b, 47b} If there exists an active hemolytic streptococcal infection, their use would seem indicated, and sulfanilamide has been given in reduced dosage without ill-effect where the blood level of the drug has been carefully watched.^{45b} Surgical measures such as mastoidectomy may become necessary for intrinsic reasons during the acute stage, but it is generally considered advisable to defer tonsillectomy or drainage of sinuses until the acute manifestations have subsided, since an exacerbation at least in the urinary findings, may follow these procedures.

The possibility exists that dietary factors may play a rôle in determining the course of the renal injury. Although clinical studies^{20, 49, 56} have failed to reveal any deleterious effects of proteins, in experimental acute renal insufficiency (produced by nephrotoxic serum,⁷² vena caval obstruction,² partial,²¹ and complete¹⁴ nephrectomy) it has been demonstrated that diets high in protein are harmful, and may, in certain, but not in all, species of rats⁷³ be responsible for progression in nephrotoxic nephritis. On the other hand, diets high in carbohydrate have been found to be beneficial.^{14, 21} The value of the alkaline-ash diet, long recommended, has been questioned.⁵³ Alcohol apparently does not aggravate the renal lesion in glomerulonephritis.¹⁶

Except for the enforcement of rest and quiet in all instances, treatment of the acute attack cannot be standardized. Individual items of therapy must be employed with a clear knowledge of the pathologic physiology in the particular case at hand. Protein should be limited especially when azotemia is of significance. The intake of fluid and salt should be restricted when hypertension and cardiac failure are prominent, but increased when azotemia is severe. Digitalis may prove useful in myocardial insufficiency.⁶⁰ Magnesium sulphate intravenously or intramuscularly (0.2 cc. of a 25 % solution per kilo) and by mouth has proven effective in reducing the blood pressure, apparently by combating vasospasm.⁶⁴ Cerebral edema and convulsions may be relieved by sedation, spinal drainage, or the administration of 50 % sucrose intravenously. Severe oliguria and anuria may be serious problems and an evaluation of the effectiveness of such measures as diathermy and the intravenous use of hypertonic sugars is difficult. The length of time that bed rest should be enforced following an attack of acute glomerulonephritis is a matter of judicial individualization. It would seem wise to advise bed rest as long as steady improvement progresses and to discontinue it only when no further improvement is apparent.

In the chronic active stage of glomerulonephritis including the nephrotic syndrome, edema is usually the most troublesome manifestation. Diets high in protein (100 to 120 gm. for adults, 3 gm. per kilo for children) are necessary in order that protein lost in the urine may

be replaced. The intake of fluid should be restricted and diuretic salts, such as ammonium or potassium chloride or nitrate, or ammonium sulphate² should be substituted for sodium chloride. The use of acacia to promote diuresis has been studied extensively,^{31-33,43,70} and found to be effective and safe if properly employed. Its diuretic effect is attributed to the increased excretion of water and chloride that follows its injection.³² It may be administered as a 6% solution of acacia in 0.9% sodium chloride,⁴³ 500 cc. or 30 gm. being given daily until a total of 120³¹ to 180 gm.⁴³ has been given. Before acacia is used, patients should be tested carefully for sensitivity.⁴³ Urticarial reactions occur in 10% of cases, are usually relieved by epinephrine and are not considered a contraindication to further therapy.³¹ More serious reactions accompanied by dyspnea and chest pain occasionally occur and are indications for discontinuance of the injection. Alarming increase in blood volume has been observed,⁴³ and fatalities following the use of acacia have been reported and attributed to liver damage and the blockage of capillaries by conglutination of red blood cells.⁷⁸ Concentrated human blood serum has been found to be an effective diuretic in nephrosis but not in other types of renal edema.³ As previously mentioned, intravenous amino-acid therapy by means of casein hydrolysate is reported to be of great value in lowering the mortality of the "nephrotic crisis."²⁴

In the terminal stage of glomerulonephritis with increasing azotemia, dietary protein should be limited and fluid intake increased, unless congestive heart failure is present. Acidosis may be relieved by the use of sodium bicarbonate and twitchings may be abolished by the injection of calcium salts.³⁶ Hyperphosphatemia with its attendant hypocalcemia may respond to diets low in phosphorus or to the oral administration of aluminum hydroxide which decreases the absorption of phosphorus from the bowel.²⁶ Therapy thus is aimed at the relief of disturbing symptoms, or, as Page has expressed it in an excellent review of the therapy of Bright's disease,⁶⁹ "treatment in the terminal stage consists first and foremost in making the patient happy."

EDWARD MATTHEWS, M.D.

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NEUROLOGY AND PSYCHIATRY.

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO SCHOOL OF MEDICINE,
DENVER, COLO.,

AND

GEORGE S. JOHNSON, M.D.,

PROFESSOR OF PSYCHIATRY, STANFORD UNIVERSITY, SAN FRANCISCO, CALIF.

ELECTRICALLY INDUCED CONVULSIONS IN THE TREATMENT
OF MENTAL DISORDERS.

IN recent years "shock" treatment of mental disorders has been both enthusiastically promoted with optimistic claims and harshly condemned as unscientific and barbaric. Careful clinical studies have somewhat deflated some of the earlier claims,³² but have at the same time indicated that shock treatment is a valuable method in a more limited sphere. It has been emphasized repeatedly that shock treatment of any sort should be only a small part of the total therapy in any case of personality dysfunction.^{9,21a,28,35}

While the perfection of certain details in procedure has decreased the immediate dangers connected with insulin^{16,32} and metrazol^{3,8,9} therapy, the serious question of the possibility of later organic brain damage is still unanswered. However, despite a lack of carefully controlled and independently verified investigations of these therapeutic instruments in experimental laboratories, widespread clinical application of shock treatment has been made and will no doubt continue for some time. The rapid development of shock therapy reflects the increased concern over the enormous personal, social, and economic importance of mental disease in general, a problem of the first magnitude.

Even with many basic problems of insulin and metrazol therapy still undecided,³² various other agents of similar nature have been given clinical trials. Among these are other convulsant drugs,⁹ inhalation of nitrous oxide¹⁴ and nitrogen,^{38,39} and the production of convulsions by the application of the electric current.

Of these, electric shock therapy is the most important and has already been given extensive clinical use in mental disorders.³⁰ Although it has been reported to present a number of advantages over other types of shock therapy, it is noteworthy that reports of therapeutic results with electric shock have tended to be more conservative than the earlier reports about insulin and metrazol. It should be understood that electric shock therapy is a form of convulsion treatment with general effects similar to those of metrazol, and that insulin treatment is a less acute, more prolonged method in which the production of convulsions is not necessarily desirable.¹⁶ Chemotherapeutic methods of shock therapy were reviewed in these columns in December, 1937,²⁸ and in December, 1939.⁹ Other excellent reviews have been published recently by Katzenelbogen³² and by Jessner and Ryan.²⁷ This paper deals primarily with electric shock therapy.

For nearly 40 years it has been known that convulsions and unconsciousness can be produced in animals by the application of electric current by various methods,⁴ and the dramatic accidents with electricity in humans are an everyday commonplace. Convulsive seizures of a restricted nature have been produced frequently in humans by direct electrical stimulation of the brain at operation. Experimentally, the use of electrically induced convulsions led to the discovery of the anti-convulsant effect of diphenylhydantoin by Putnam and Merritt in 1938.⁴⁶

The first therapeutic use of convulsions induced by electric current was reported in 1938 at the Medical Academy in Rome by Cerletti and Bini, following animal experiments to determine a safe method.^{6a} Since introduction of the treatment into England in the following year and more recently into this country, several different types of apparatus have been devised, but all are essentially the same in principle.^{11,13,45,50,51}

Current is passed through the fronto-temporal regions by way of large metal electrodes held firmly in place on each side of the head by means of either a tight rubber band or large forceps resembling ice tongs. Ordinary 110 volt alternating house current may be used as the source; the voltage is regulated by transformers, and the duration is regulated by an automatic timer.

For optimal conduction electrode jelly is vigorously applied to the scalp, and the electrodes are covered with cloth jackets soaked in strong (20%) salt solution. The centers of the electrodes should be placed not further back than the coronal suture and the edges should not extend below the orbito-meatal line. The electrodes should be as far apart as possible within these limits. This site of application has been found to be the most satisfactory;^{24b} it is believed that the frontal adverse field (area 6aB of Vogt and Brodmann) is the area with the lowest convulsive threshold.^{13,29} Application further back might lead to undesirable medullary stimulation, and application further forward has been found to be less efficient.^{24b} Large electrodes with an area of 30 to 100 sq. cm. are used to prevent burning of the scalp and are also thought to be more efficient than smaller electrodes.^{24b,30}

Before application of the shocking current the intactness of the apparatus is tested by the passage of current through an "artificial head," a conductor of known resistance. Then a trial current of very low voltage (0.5 to 1 volt), imperceptible to the patient, is passed through the patient's head to determine the relative resistance of the head. The apparent resistance as measured in this manner ranges from 400 to 2000 ohms; a resistance of more than 2000 ohms usually indicates inadequate contact between the electrodes and the scalp.⁵¹ The actual resistance of the head during the passage of the higher voltage shocking current is known to be considerably lower than the resistance determined beforehand with the low voltage testing current.^{20,24b,30,51}

This alteration of the resistance is believed to be due to changes in the superficial tissues of the head brought about by the higher tension current.^{24b} It has been shown that patients with initially high resistance have a proportionately greater fall in resistance than patients whose resistance is initially rather low.^{24b}

No true correlation exists between the initial resistance readings and the convulsion threshold of the patient. Most patients show a slight

day-to-day variation in threshold, and it is usually necessary to increase the dosage of current slightly during successive treatments.²⁶ The amount of electricity may be regulated by changing either the voltage or the duration of the shock.

The usual voltage range varies from 70 to 150 volts, and the duration of exposure varies from 0.05 to 2 seconds. The amount of current passed through the head varies from 300 to 1000 milliamperes, but it is said that only about one-hundredth of this amount actually reaches the brain.^{24b} A voltage of less than 60 produces a stimulus so small that the patient does not lose consciousness and may feel the shock. Although shocks of much higher voltage and longer duration than any obtainable with the usual apparatus may result in serious damage of the brain,^{6a, b} it is believed that no harm results from using an overstrength stimulus within the above maximal voltage and duration.^{24b}

The course of treatment is usually started with a setting of 80 to 130 volts at 0.1 to 0.2 second. If a satisfactory seizure occurs, the same setting may be used the next time. If no convulsion at all occurs, another stimulus may be given immediately with increased voltage or duration, successively stronger shocks being given until a convulsion is induced. Hemphill and Walter^{24b} have given as many as six shocks in succession without mishap. Rare patients have a very high convulsion threshold (up to 150 volts at 0.6 second), but it is practically always possible to secure a convulsion. It is never necessary to use a setting of greater than 150 volts.

With proper procedure there is always instantaneous and absolute loss of consciousness following the application of the stimulus.^{26, 48a} An inadequate stimulus produces an "absence" or stunning reaction. This may consist merely of momentary unconsciousness with a sudden start but no muscular contractions; the patient may experience some peculiar sensation such as "flashes of light" but feels no pain.² A larger but still subconvulsant stimulus produces a "petit mal" reaction, characterized by a sudden start and immediate unconsciousness for 5 to 40 seconds, with occasionally facial twitchings, coarse arm and leg tremors, apnea, cyanosis, and confusion of brief duration.

The "grand mal" convulsion type of reaction closely resembles a true epileptic seizure and is similar to a convulsion produced by metrazol but is of shorter duration and lesser severity. There is an immediate loss of consciousness and a start, a sudden marked generalized flexion movement, thought to be due to direct stimulation of the motor cortex. A cry occurs frequently but not always. The generalized tonic spasm, which lasts from 10 to 25 seconds, may occur immediately or, less commonly, following a latent period up to 30 seconds.

The clonic phase, lasting from 10 to 30 seconds, then ensues. The pupils become widely dilated, and there is conjugate deviation of the eyes. During the convulsion the patient does not breathe and usually becomes very cyanotic. The total apneic period is usually less than a minute, and delayed resumption of respiration is quite rare.⁴⁹ Incontinence is rare; ejaculation has also been reported. After the convulsion there is a short period of deep stupor, often with sucking or biting movements, and then a period of confusion, seldom lasting longer than 10 minutes.

For a short period following the convulsion there is usually a moderate

rise in the systolic blood pressure and a tachycardia which is occasionally followed by a bradycardia. Ankle clonus is almost always present, and Hoffmann's and Babinski's signs frequently appear for a few minutes. The blood sugar usually rises about 50 %, the red cell count and hemoglobin are slightly elevated, and the white cell count may be doubled soon after the convulsion; these changes usually return to the previous level within $\frac{1}{2}$ hour. There is always a marked increase in the lactic acid content of the blood after a convulsion,^{21a,27} undoubtedly due to the muscular activity.

There is always a complete amnesia for the period of treatment.³³ Some patients have a complete retrograde amnesia during which they are unable to recall any event which transpired during a period of 2 or 3 hours preceding the shock. In others, this amnesia is partial or insular in type, while some patients have only a mild and transitory amnesia of events immediately preceding the shock.³³ Some patients also show a patchy impairment of memory separate from the amnesia associated with the treatments. This memory loss is usually transient and does not disturb the patient, although occasionally it may last as long as 2 months after the last treatment.¹⁹

Preparation of the patient for the treatment is relatively simple.³⁰ The treatment is usually given in the morning, and breakfast should be withheld, although nausea and vomiting following electric shock treatment are much rarer than following metrazol. The bladder and bowels should be evacuated before the treatment. If a sedative drug is administered during the night preceding a treatment, the convulsion threshold may be raised.^{24a,48b} It is not necessary to shave the patient's head, but all hairpins and other metal objects should be removed. A mouth gag should be inserted initially to prevent biting of the tongue, and artificial dentures should be removed. The assistants who hold the patient are in no danger of receiving a shock, providing the patient's head is not touched during the passage of current, and that they are standing on a dry floor.

To prevent fractures and dislocations the treatment is given with the patient reclining on a hard, flat non-metal table or couch, free of moisture. A small hard pillow or sandbag is placed under the mid-thoracic region of the spine, while the patient's shoulders, hips, and knees are fixed to the table by firm pressure.

This method of spinal hyperextension has been found to reduce considerably the incidence of vertebral fractures in patients treated with metrazol.^{8,18,22} Curare has been employed most successfully for the prevention of fractures in metrazol therapy, but Kalinowsky and his coworkers³¹ advise against the use of curare for this purpose because electric shock treatment has—contrary to metrazol—a depressant effect on the respiratory center. Furst and Stouffer,¹⁹ however, report the use of curare without mishap in 5 electrically treated cases.

The optimal frequency and total number of treatments in a course are as yet undecided. Most workers recommend that the treatment be given 2 or 3 times a week up to a total of 10 or 15 treatments. Furst and Stouffer¹⁹ state that despite improvement after 3 or 4 treatments, the course should be continued to 10 in order to "fix" the result. Gonda^{21a} believes that more treatments may be necessary to schizophrenics than in depressed patients, and advises 20 or more shocks in

schizophrenics, even though improvement has appeared after a few treatments.

Sogliani⁴⁹ describes cases in which the improvement started only after the 30th convulsion and some even later. Both Sogliani and Fumarola¹⁷ have given some patients repeated convulsions in a single day in an effort to reduce the duration of the course of treatment. Hemphill and Walter^{24b} see no harm in giving the treatments daily for 60 or more days in some cases while there is any hope for more improvement.

On the other hand, Myerson⁴⁴ believes that as few shocks as possible should be given, that only 3 or 4 treatments may be required for a complete remission in some patients with depression. Ziskind's work with metrazol indicates that a course of 2 treatments a week for 6 to 8 weeks carries little danger of memory impairment, and 3 treatments a week should not be given for longer than the first 2 weeks.⁵⁴

So far, reports on the results of electric shock therapy show no essential differences from the recent results with metrazol.^{36,44,47,49} The best results have been obtained in depressions, with only fair results in acute schizophrenia. Most observers have reported more than 70% or 80% remissions or marked improvement from depressions.^{7,19,21a,42,44,53} Good results have also been obtained in the small number of manic patients treated by different workers.^{24b}

Sogliani⁴⁹ reported "recovery" in 12 out of 15 schizophrenics with illness of less than 1 year's duration, but in only 3 out of 55 cases of more than 1 year's duration. As with metrazol, the best results have been reported in the catatonic group, but in all types of schizophrenia early relapses have occurred in a large percentage of cases.⁴⁷ Wyllie⁵³ obtained "immediate improvement" following electrically induced convulsions in 14 out of 18 schizophrenics, but in only 2 cases was the improvement maintained for as long as 2 months.

Others have reported remissions varying from 21% to 80% in cases of schizophrenia of recent onset.^{19,21a,31,42} It is generally agreed that results with chronic cases are much more unfavorable, but some advise the use of electric shock therapy in chronic institutional cases of schizophrenia to facilitate their general management.^{24b,31} Such reports indicate that electric shock, as well as metrazol, is probably not a very useful type of treatment for schizophrenia, except that in some cases it may bring about a change which facilitates other forms of therapy and accelerates recovery.

No deaths have been reported yet from more than 10,000 electric shock treatments.³⁰ The complications and contraindications are apparently similar to those for metrazol. Exacerbation of chronic pulmonary tuberculosis has been the chief cause of death following metrazol therapy.^{5,34} Although this is unexplained, there is no reason to believe that electric shock therapy will be less dangerous in this respect. Fractures and dislocations have been reported following electric shock therapy,^{7,20,21a,b,53} but less frequently than after metrazol, probably because of the somewhat milder character of the convulsions.

The treatment is contraindicated in the presence of active or recently healed pulmonary tuberculosis or other disease of the lungs, any febrile illness or acute infection, arthritis of the spine, marked hypertension

or arteriosclerosis, serious cardiac disease, nephritis, or organic disease of the central nervous system.^{7,24b} These contraindications may have to be modified in individual cases with mental conditions so desperate as to threaten life.

Aside from the lessened danger of fractures, dislocations, and muscle injuries, electric shock therapy has a number of other advantages over metrazol.^{1,6a,6,11,15,21a,26,48b,49} Other complications are also less frequent: headache, nausea and vomiting, and severe psychomotor excitement are quite *uncommon after electric shock*.

The milder nature of the convulsions with electric shock produces less strain on the cardiovascular system than either insulin or metrazol. Bellet, Kershbaum, and Furst² studied the electrocardiograms of 50 patients with 100 electric shock treatments and found only minor changes, except 2 records of older patients in whom more serious signs were encountered.

Another marked advantage is the absence of the "fear" reaction or aura which invariably occurs with metrazol during the latent period between the injection and the loss of consciousness and also prominently with subconvulsant doses.^{21a} However, despite the complete amnesia for the electric shock and absence of a fearful aura, some patients dislike the treatment because of their ignorance about what has happened to them, but seldom object greatly to subsequent treatments.^{44,53}

Most patients are more coöperative in electric shock therapy than with metrazol. An uncoöperative patient can be "stunned" by a preliminary subconvulsant shock in order to facilitate proper holding for the treatment itself.

The difficulty in making an intravenous injection in an uncoöperative patient or in one with inaccessible or thrombosed veins, so common in metrazol therapy, is entirely escaped by electric shock. The effects of a blood-borne drug are avoided, and delayed reactions, not uncommon following metrazol, are very rare after electric shock, although a few serious delayed reactions have been reported.^{2,41} After the instrument is purchased initially the cost of the treatment is negligible, and as many as 15 or 20 patients can be treated in 1 hour.^{24b}

These advantages of electric shock therapy constitute in themselves a serious but indirect danger, if the method is to be put into indiscriminate and promiscuous use by unqualified and misguided therapists. Shock treatment in general is still in an experimental stage with an uncertain future.^{10,37} All forms of shock treatment are believed to produce qualitatively similar types of organic brain damage in animals.^{23,52a}

Weil and Liebert^{52a,6} reported marked glial changes and mild neuronal lesions in the brains of 6 patients who had received metrazol treatments several months previously, and also found similar disturbances in the brains of rabbits subjected to either metrazol or insulin treatments. Finley and Brenner¹² observed similar lesions in the brains of monkeys treated with insulin or metrazol.

Bini⁴ found widespread and severe but mainly reversible changes of the cortical nerve cells of animals subjected to electric shock similar to that used in treating humans. Heilbrunn and Liebert²³ made biopsies of brains of rabbits at intervals following convulsions produced by various agents. They found that the changes in the ganglion cells

were more severe following electric shock than after metrazol, insulin, camphor, or nitrogen gas. They also noted that reversal of the morphologic alterations occurred more slowly after a second or third convulsion than after the first.

Studies of electroencephalograms of humans and animals indicate that changes in cortical activity are usually of shorter duration and milder following electrically induced convulsions than after metrazol convulsions.^{1,13,25,40} However, it was noted by Hughes, Wigton, and Jardon²⁵ that after successive convulsions during a series of treatments, abnormal electroencephalographic waves persist for longer periods, so that after 6 or 7 treatments they may be observed for several days and occasionally may not entirely disappear for 2 or 3 weeks after the last treatment. Such observations show the need for much more clinical and experimental studies of similar nature.

The possible efficacy of subconvulsant or petit mal shocks should also be considered.^{19,43} A few observers believe that some patients may be made worse instead of being helped by subconvulsant shocks.⁵⁰ Electric shock has also been used as an outpatient procedure with apparent safety.^{24b,44,50} This practice should not be adopted generally until the effects of the treatment are better known. Patients whose conditions justify such a form of treatment ordinarily should require hospital care.

Electric shock will probably largely replace metrazol as a form of convulsion therapy.^{19,43} This type of treatment is chiefly indicated in depressed states; its value in manic reactions is less certain. In schizophrenia its usefulness is quite limited. The use of such a drastic method in the treatment of the ordinary types of psychoneurosis is not justified in the present state of our knowledge of remote effects.

LEON J. WHITSELL, M.D.

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PHYSIOLOGY.

PROCEEDINGS OF

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SESSION OF NOVEMBER 18, 1941.

Labyrinth and Cerebellum. E. SPIEGEL and N. SCALA (Department of Experimental Neurology, Temple University School of Medicine). The following observation may shed some light upon cerebello-labyrinthine relationships.

After inducing a lesion in parts of the cerebellum of cats, particularly in the lobus posterior medianus, with the vestibular nuclei and their fiber systems histologically intact, nystagmus was observed in abnormal positions of the head, particularly in supine position with the vertex downward. When nystagmus in normal position of the head was weak, it was increased, sometimes also its direction was changed, in abnormal positions. In some cases nystagmus appeared in abnormal positions only. This phenomenon is transient. Electrolytic lesions of the nuclei

teci had a similar effect. In analyzing the receptor mechanism, neck reflexes and retinal reflexes could be excluded. Bilateral labyrinthectomy abolished this effect of position, while a weak spontaneous nystagmus could persist. It is assumed that the appearance of positional nystagmus following cerebellar lesions is a phenomenon of release of parts of the vestibulo-ocular reflex arcs, since it is associated with increase of the experimental postrotatory nystagmus.

Periodicity of the Excitatory Process in Nerve. FRANK BRINK and D. W. BRONK (Johnson Research Foundation, University of Pennsylvania). The cellular mechanism which determines the time interval between propagated impulses in chemically excited nerve cells was studied. Arvanitaki has reported (*Arch. internat. de physiol.*, 49, 209, 1939) the existence of localized periodic changes in electrical potential at the site of initiation of propagated impulses. In the present experiments, it has been shown that when the calcium and magnesium are removed from the fluid bathing a restricted length of the giant axon of a squid, such periodic electrical discharges occur as the first evidence of excitation at a time when there are no conducted impulses. These local periodic potentials increase in amplitude until, finally, conducted impulses are initiated at the same frequency as the previously initiated local response. Thus the intervals between impulses in a train are determined by a periodic excitatory process that exists independently of the conducted impulses. Adrian's hypothesis that such intervals are determined by a process of recovery from a previous impulse must therefore be reconsidered.

When the calcium was removed from the fluid bathing a limited portion of a myelinated nerve fiber (Type A) a train of propagated impulses was initiated. The time intervals between successive impulses were not always equal. The larger intervals were shown to be approximately integral multiples of the shortest or fundamental period. The departure from the exactness of this rule was related to the random variations in the fundamental period of the excitatory process. It is assumed that this fundamental period of the conducted impulses in these fibers is determined by the periodicity of a local excitatory process similar to that observed directly in giant fibers from squid.

The Effect of Vagotomy on the Secretory Response of the Pancreas to Peptone. J. O. CRIDER and J. E. THOMAS (Laboratory of Physiology, Jefferson Medical College of Philadelphia). The presence in the intestine of products of protein digestion increases the flow of pancreatic juice through a mechanism other than secretin (*Am. J. Physiol.*, 134, 656, 1941). Presumably a reflex affecting the secretory nerves is involved. In an effort to trace the reflex pathway, dogs were prepared in which either both cervical vagi were chronically exposed or one vagus was cut and the other exposed. In such animals injection of peptone solution into the duodenum had the usual effect of increasing the rate

of secretion of pancreatic juice. After the vagi were blocked by injection of cocaine or proeaine into the exposed nerve trunks or by cutting the remaining intact vagus (in 1 animal) peptone, administered as before, failed to increase the flow of pancreatic juice. The conclusion is drawn that peptones stimulate pancreatic secretion through a reflex are involving the vagus nerves.

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ORIGINAL ARTICLES.

THE USE OF SULFANILAMIDE IN THE TREATMENT OF ACUTE
GLOMERULAR NEPHRITIS.

BY ROBERT H. WILLIAMS, M.D.,

INSTRUCTOR IN MEDICINE, HARVARD MEDICAL SCHOOL; ASSISTANT PHYSICIAN, THORNDIKE MEMORIAL LABORATORY; JUNIOR VISITING PHYSICIAN, BOSTON CITY HOSPITAL, BOSTON, MASS.

WARFIELD T. LONGCOPE, M.D.,

PROFESSOR OF MEDICINE, SCHOOL OF MEDICINE, JOHNS HOPKINS UNIVERSITY; PHYSICIAN-IN-CHIEF, JOHNS HOPKINS HOSPITAL, BALTIMORE, MD.,

AND

CHARLES A. JANEWAY, M.D.,

INSTRUCTOR IN MEDICINE, IN BACTERIOLOGY AND IN IMMUNOLOGY, HARVARD MEDICAL SCHOOL; ASSOCIATE PHYSICIAN, PETER BENT BRIGHAM HOSPITAL, BOSTON, MASS.

(From the Medical Clinic, the School of Medicine, Johns Hopkins University and Hospital.)

It has been many years since Loehlein⁹ in 1907 presented evidence to show that acute glomerular nephritis was the direct result of streptococcic infections. Since then the question has been the subject of much discussion, and though it is now generally recognized that infections by hemolytic streptococci precede with great frequency the onset of acute glomerular nephritis, the exact relationship between the two has never been accurately defined.^{3-5,12a,c,13,19,22,24} Evidence, however, has been presented to show that a continuation of the infection or recurrent infections due to hemolytic streptococci predisposes to a progression of the nephritis and is the prime factor in preventing recovery or in leading to chronic nephritis.^{12a,c,13,18,24}

The great regularity with which a marked increase in the anti-streptolysin content of the blood serum occurs during the course of acute glomerular nephritis,^{12b,14,17} even when cultures from the pharynx or other foci of infection fail to show hemolytic streptococci, is an additional argument in favor of the close association between this particular form of infection and acute hemorrhagic nephritis.

These facts do not, however, exclude the possibility that other bacteria, such as the *Streptococcus viridans*, the pneumococcus or the gonococcus may be concerned in the origin of some instances of acute nephritis. Indeed, there is reason to believe that they do so, though infections by these organisms are probably concerned with the origin of a comparatively small proportion of cases.

Since the persistence of infection may be of great importance in determining the course of the nephritis much emphasis, during the last few years, has been placed on the elimination of foci of infection. It has been necessary to rely largely upon such surgical measures as removal of tonsils and adenoids, or the drainage of infected paranasal sinuses to accomplish this. The efficacy of these surgical procedures has been questioned,^{6,16} and has rarely been attended by brilliant results, for it has often been impossible by these means alone to cure completely the infection.

The great value of effecting complete cure of the acute nephritis lies in the fact that once the nephritis has healed, a recurrence rarely if ever occurs, even though the patient experiences one or more serious infections due to the hemolytic streptococcus.^{8,12a,c} If, on the other hand, the disease persists, even in quiescent form, subsequent infections by hemolytic streptococci are liable to cause acute and sometimes serious exacerbations of the disease.^{12a,c,13,18,24} Until the introduction of chemotherapy, therefore, the available treatment consisted principally in prolonged rest, diet, and surgical removal of the foci of infection. But with the demonstration of the highly effective action of sulfanilamide upon the hemolytic streptococcal infections, the possibility of using this chemical to combat infections associated with acute hemorrhagic nephritis naturally came to mind.^{12d} A series of 42 cases of acute nephritis have therefore been treated, during the acute phase of the disease, with sulfanilamide. The effect upon the infection and the later course of the nephritis in these patients has been contrasted with 108 cases of acute nephritis which had not been treated with sulfanilamide.

The work was started at a time when sulfanilamide was the only chemical available for the treatment of infections caused by hemolytic streptococci. Its efficacy for this purpose had been amply demonstrated. The work of Marshall, Cutting and Emerson¹⁵ had shown, moreover, that administration of large amounts of the drug exerted no harmful effect on the kidneys of dogs, and a vast number of subsequent observations in the human being have upheld these conclusions. It is, however, well recognized that sulfanilamide is not as rapidly excreted in the presence of even slight disease of the kidney as it is in the normal individual, and the drug is prone, therefore, to accumulate in comparatively high concentration in the blood even when the form of nephritis is mild. Since these studies were started three other drugs, namely sulfapyridine, sulfathiazole and sulfadiazine, have come into use. In spite of their efficacy, it

seemed highly undesirable to employ them for the treatment of any infection associated with nephritis, for both sulfapyridine and sulfathiazole are known to damage occasionally the kidneys either through the excretion of the acetylated form in crystals or by direct action upon the cells of the organ. Though sulfadiazine may be less likely to produce these injurious effects, experience has not been sufficiently extensive with this drug to warrant its use in patients suffering from nephritis.

In December, 1936, we began to use sulfanilamide in treating patients with acute glomerular nephritis. It has been employed almost exclusively in those patients from whom beta hemolytic streptococci have been cultured from some focus. We have treated only those patients who had a well-defined acute onset of their nephritis and only those who were admitted to the hospital within 2 months of this onset. In most instances they were admitted within a few days after the disease had manifested itself. We now have treated 42 such patients. The nephritis was regarded as mild in 11 cases (26%), moderately severe in 16 (38%), and severe in 15 (35%). Some of these patients exhibited marked albuminuria, hematuria, cylindruria, low renal function, azotemia, hypertension and edema. In 25 instances the nephritis followed acute tonsillitis, in 4 sinusitis, in 5 skin infections, in 1 scarlet fever, and in 2 puerperal infection. In some patients there was more than one focus. The interval from the prodromal infection to the onset of the nephritis averaged 13 days. The interval from the time the nephritis had manifested itself until sulfanilamide was administered varied in different cases from 1 to 173 days but averaged 26 days and in 27 cases was less than 14 days.

In order that we might evaluate the manner and extent to which the sulfanilamide therapy modified the course of acute hemorrhagic nephritis in these patients we have analyzed for control the records of 108 patients fulfilling all the requirements which we have presented above whom we have followed since 1925. We have selected at random 70 of this group and tabulated the course in great detail. This group has had essentially the same clinical and bacteriologic studies and the treatment has been similar in every way except that they did not receive sulfanilamide. The extent of the nephritis in 70 patients of this group was found to be mild in 17 cases (24%±), moderate in 24 (34%±), and severe in 29 (41%±). Thus it may be seen that the severity of the disease in the treated and untreated groups is comparable. The interval from infection to the onset of nephritis was found to average 10.3 days as compared with 13 days in Group I. (Throughout this paper we shall refer to the control group as Group II and to the ones receiving sulfanilamide as Group I.)

The dosage which we have prescribed for our patients has varied from 1.2 to 6 gm. per day. The commonest dose, however, was a

total of 2.4 or 3.6 gm. divided into 6 equal doses at 4-hour intervals. The total amount of the drug given to any patient has varied from 6 to 169 gm. (average 49 gm.). The drug was administered over a period of 3 to 63 days (average 17 days). The blood concentration was followed in 32 patients and was found to vary from 4.5 to 18 mg. per 100 cc. In 13 subjects the level reached 10 mg. per 100 cc. at some time during the therapy. It was found that there was a greater variation, from day to day, of the blood concentration of the chemical than we have observed in subjects treated for other (non-renal) conditions. This has been attributed to the frequently changing renal function.

Since Southworth²⁰ found that acidosis may develop in association with sulfanilamide therapy we have usually given 0.6 gm. of sodium bicarbonate with each dose of the former. This has been used in spite of the fact that many of our patients have been edematous. No attempt was made to limit the fluids to any extent greater than was necessary to control the edema.

TOXIC REACTIONS DUE TO SULFANILAMIDE. Mild toxic reactions characterized by headache, nausea, or vomiting developed in 3 patients. Seven patients developed fever and 2 a slight anemia. The drug was promptly discontinued in each of these instances and the symptoms rapidly abated. Occasionally difficulty was encountered in differentiating the symptoms of the nephritis from those of sulfanilamide intoxication. No serious complications were encountered.

Results of Therapy. FOCI OF INFECTION. In view of the great importance accorded to the acute infections which precede the development of nephritis it naturally was of interest to determine whether sulfanilamide had been effective in combating such infections. In our studies we have paid particular attention to the beta hemolytic streptococcus, as this organism is apparently the one of etiologic significance in by far the great majority of the cases. Table 1 and Figure 1 show the results of some of the throat cultures which have been made. It is quite noteworthy that whereas 71% of the patients in Group I had positive throat cultures just before sulfanilamide was begun, only 15% yielded positive cultures shortly after its discontinuance. This incidence is little more than is found in normal individuals in Baltimore in the winter months.¹¹

It may be observed that, on admission, the throat cultures were positive for beta hemolytic streptococci in 76% of the patients in Group I and in 85% of the ones in Group II. Some subjects had several foci containing these organisms. They were obtained from the throats of all but 7 patients in Group I before sulfanilamide was started. In 2 of the 7 they were cultured from a skin infection, in 1 from an infected sinus and in 1 from the uterus. At the time of discharge from the hospital the infection in these subjects had cleared up and the number of patients giving positive throat cul-

tures was decidedly less, being 15% in Group I and 26% in Group II. It should be mentioned here that this change has been aided to a large extent by the performance of tonsillectomies in more than one-half the cases, by the drainage of infected sinuses in several instances, by the extraction of teeth with periapical abscesses, and by other similar procedures.

TABLE 1.—NUMBER OF PATIENTS FROM WHOM BETA HEMOLYTIC STREPTOCOCCI WERE RECOVERED ON THROAT CULTURE. *

	No. +.	No. neg.	Total.	Positive, %.
On admission:				
Group I	29	9	38	76.3
Group II	58	10	68	85.0
Before sulfanilamide:				
Group I	27	11	38	71.0
After sulfanilamide:				
Group I	5	28	33	15.0
On discharge:				
Group I	5	27	32	15.6
Group II	15	42	57	26.3
Six months later:				
Group I	5	20	25	20.0
Group II	11	32	43	26.6

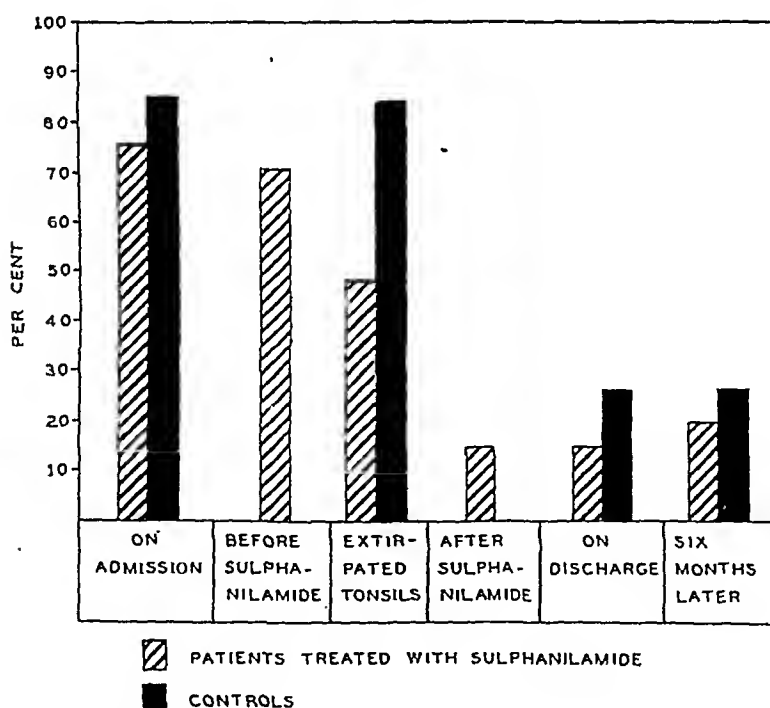


FIG. 1.—Percentage of patients with beta hemolytic streptococci in throat cultures.

We were permitted to repeat the throat cultures 6 months later on 25 subjects in Group I and on 43 subjects in Group II. Positive cultures were obtained in 20% of the former and 28% of the latter.

Of greater concern than the throat cultures was the incidence of organisms in the tonsils. The latter were removed from 38 patients

in Group II. The tonsils of 32 of these patients were macerated and cultured for beta hemolytic streptococci. The cultures were found to be positive in 27 subjects (84%). Tonsillectomy was performed on 29 patients in Group I. Cultures were made from 28 subjects, 13 (47%) of which yielded positive cultures. This incidence was found to be higher than we had at first anticipated, though it is considerably lower than that of the untreated patients. It is quite important to point out that sulfanilamide had not been administered, unfortunately, for at least a week preceding tonsillectomy, in 12 of the 28 subjects. Nevertheless, it is now known that the administration of relatively large doses over long periods of time may not render the tonsils sterile. We have regarded the persistence of these organisms as being responsible for some of the flare-ups which we have witnessed.

Colebrook and Purdie² have reported that hemolytic streptococci were recovered from cervical swabs taken on discharge from the hospital in 39 of 81 (48%) of their cases of puerperal infection that had recovered under sulfanilamide, and that 6 of 35 patients (17%) still showed positive cultures for hemolytic streptococci 3 to 6 weeks later. In experimental infections, Levaditi and Vaisman,⁷ Long and Bliss,¹⁰ and Colebrook and his associates² have reported the persistence of latent foci of hemolytic streptococci in mice treated over long periods with sulfanilamide. It is for these reasons that the various surgical methods have continued to be employed with equal vigor as in the past.

CHANGES IN THE ANTISTREPTOLYSIN TITER. Since 1930, we have made rather frequent determinations of the antistreptolysin titer of the serum. In Figure 2 the titers of antistreptolysin of both groups are recorded during the course of the disease. On admission the titer in Group I was found to vary from 50 to 500 units with an average of 198 and was over 100 in 27 of 31 subjects. The titer in Group II was within the same range, though not quite as high, varying from 16 to 500 with an average of 168, and being over 100 in 21 of 33 subjects. The average level in Group I, at the time sulfanilamide was started, was 223 units. On the completion of the treatment the average level was 239 units. At the time of discharge the titers were found to remain high in Group I, ranging from 50 to 500 units with an average of 199 and being over 100 in 27 of 30 subjects. In Group II it was found to vary from 16 to 1666 with an average of 222 and was over 100 in 21 of 33 patients.

Thus it may be stated that in spite of what antibacterial effect the sulfanilamide may have exerted upon the streptococcus, the immunologic reaction, as exhibited by the antistreptolysin titer, continued to develop in the usual manner. There was an actual increase in the titer during treatment with the drug. The titer was lower at discharge than on admission in 9 of 27 subjects (33%) in Group I, and in 11 of 32 subjects (34%) in Group II. It had in-

creased in 11 of 27 subjects (40%) in the former group and 15 of 32 (47%) in the latter.

The titer was again determined in some of the patients approximately 6 months later. With the improvement of the nephritis in most of the patients, and the recovery in some, there was found a marked decrease in the number of units in each group. In Group I the titer was found to vary from 25 to 333 units with an average of 131, and in 16 of 29 patients it was over 100. The results in Group II were found to show essentially the same decrease in the titer, but it is, indeed, worthy of mention that whereas in Group II, during the 6 months following discharge, there was a rise in titer in 5 of 23 subjects, in Group I there was a definite decrease in the titer in every patient.

EFFECT ON THE KIDNEYS. (a) *Changes in Urinary Findings.* On admission 99% of the subjects in each group had albuminuria. In most instances this was marked. Comparisons of the urinalyses before and after sulfanilamide therapy show that there was a very slight increase in the albuminuria in 2 cases. The remainder exhibited a marked decrease. This improvement continued in all but 1 patient after sulfanilamide was stopped. At the time of discharge there was a great reduction in the number of patients showing albuminuria. As shown in Figure 2, only 31% of the ones who had received sulfanilamide showed albuminuria as contrasted with 61% in Group II.

TABLE 2.—CHANGES IN URINARY FINDINGS.

	4+.	3+	2+.	+	I.	0.	Total +.	Total.
	<i>Albumin.</i>							
On admission:								
Group I . . .	8	9	9	7	4	1	37	38
Group II . . .	25	15	14	9	6	1	69	70
On discharge:								
Group I . . .	0	0	1	2	9	26	12	38
Group II . . .	6	3	3	12	19	27	43	70
Six months later:								
Group I . . .	0	1	2	6	5	19	14	33
Group II . . .	2	4	2	9	19	19	24	45
	<i>Formed Elements.</i>							
On admission:								
Group I . . .	24	6	6	0	2	0	38	38
Group II . . .	38	9	14	8	1	0	70	70
On discharge:								
Group I . . .	0	1	5	12	9	11	27	38
Group II . . .	8	3	14	13	16	16	54	70
Six months later:								
Group I . . .	1	2	4	4	3	19	12	33
Group II . . .	2	6	7	7	11	22	33	55

Not only was there a reduction in the incidence, but also in the degree of albuminuria. In no patient in Group I was this greater at discharge than on admission. This did occur, however, to 1 patient in Group II. Urinalysis 6 months later showed a slight

increase in albuminuria in 6 of 33 patients (18%) in Group I, whereas of 55 subjects in Group II there was a slight increase in 17 (31%), moderate in 1 (1.8%) and marked in 2 (3.6%).

On admission, every patient in each group showed formed elements in the urine and usually in large quantities. Comparison of this finding before and after sulfanilamide therapy demonstrated a very slight increase in 1 subject, but a decrease, marked in most instances, in the others. The improvement continued, except in 3 patients, throughout the remainder of the stay in the hospital. However, the number of formed elements in the urine at the time of discharge was much less than on admission in all of the patients in Group I. In contrast, there were 5 (7%) in Group II who showed an increase, this being slight in 4 and moderate in 1. As may be seen in Figure 2, there was a fair number of patients in

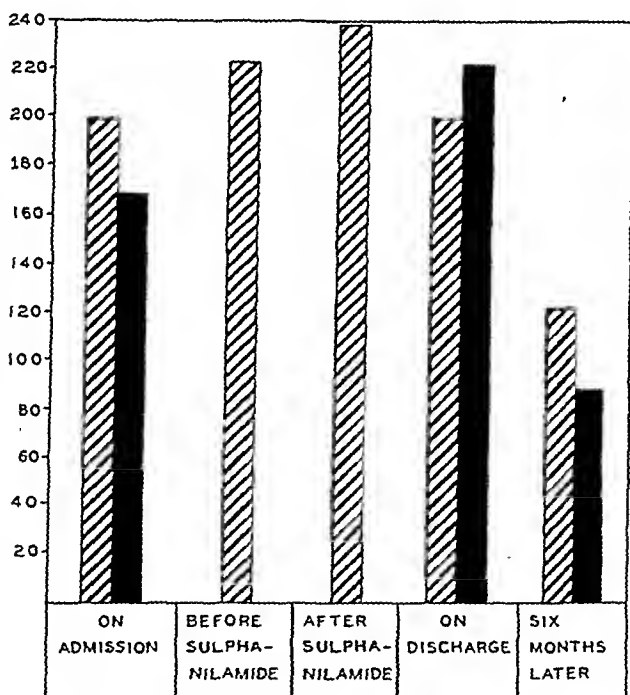


FIG. 2.—Units of antistreptolysin in blood serum.

each group whose urine became free of formed elements. It may also be noted that at the end of 6 months several others had entered this category. Of 33 patients in Group I examined at the end of 6 months there was a slight increase in the formed elements in 7 and a moderate increase in 2. Of 55 patients in Group II, 8 showed a slight increase, 4 moderate and 1 marked.

There were 9 (24%) of the patients in Group I who showed no

albumin nor formed elements at the time of discharge. In comparison there were 10 (14%) in Group II. At the time of discharge, there was more than 1+ albuminuria or 1+ formed elements in the urine of 7 (18%) of the 38 patients examined in Group I, and 28 (40%) of 70 in Group II. At the end of 6 months there was no albumin nor formed elements in the urine of 15 (45%) of 33 patients in Group I, as compared with 12 (22%) of 55 in Group II.

A common observation following tonsillectomies is to note an increase in the amount of formed elements and albumin in the urine. This is sometimes quite marked. In our control group of 70 patients tonsillectomies were performed on 38. In 29 (75%) of these there was a definite exacerbation (usually transitory) in the nephritis, being marked in 6, moderate in 15, and mild in 8. The subjects who received sulfanilamide offer a striking contrast to this in that exacerbation occurred in only 4 (14%) of the 29 patients who had tonsillectomies. The reaction was severe in 1, moderate in 1, and mild in the other 2. Worthy of mention is the fact that 3 of these patients had received no sulfanilamide for a month preceding operation. It should also be pointed out that the total intake of the drug was below average (49 gm.), being 18 gm. in 1 case and 27 in the other 2.

(b) *Renal Function.* The urea clearance was found to be impaired to about an equal extent in the two groups at the time of admission (Fig. 3, Table 3). This test showed that the renal function did not decrease in association with the sulfanilamide treatment

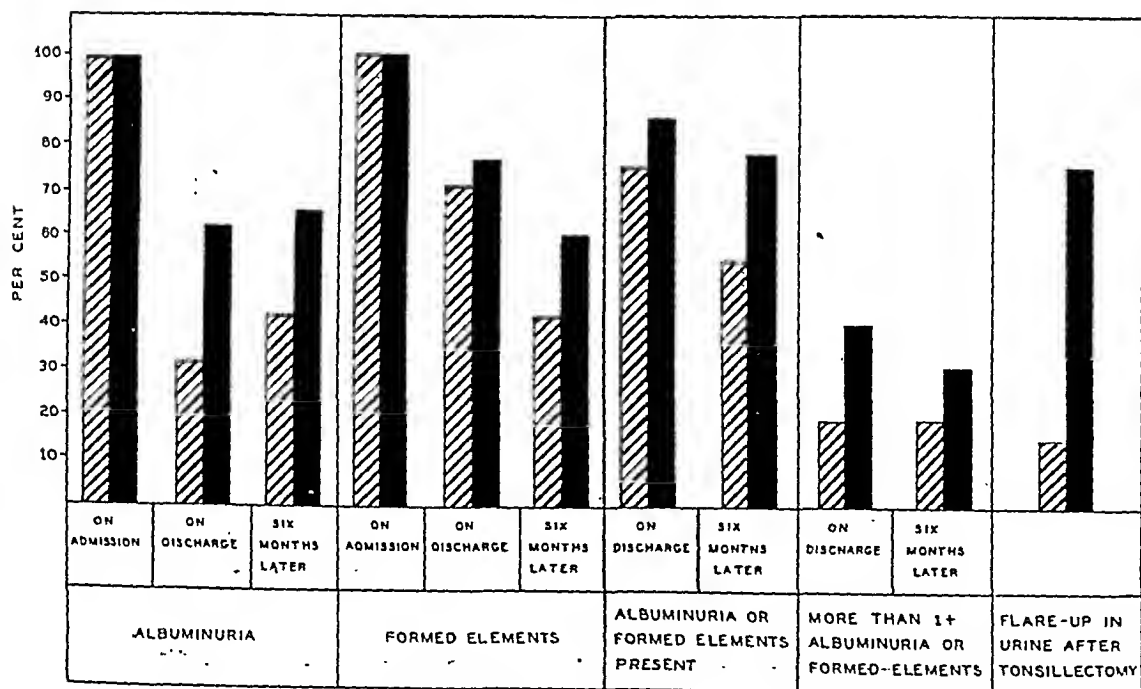


FIG. 3.—Percentage of patients showing albumin or formed elements in the urine.

in any instance. Indeed, before this therapy was started there were only 24% of the patients with a clearance above 75% of normal, whereas on the completion of this treatment there were 42%. At the time of discharge there had occurred a further improvement in each group, 48% in Group I having a function above 75%, as compared with 40% in Group II; at the end of 6 months this degree of function had been attained by 58% in the former group, as contrasted with 33% in the latter.

TABLE 3.—CHANGES IN UREA CLEARANCE.

Per cent of normal.	Less than 35.	35-45.	45-55.	55-65.	65-75.	75+.	Total.
On admission:							
Group I	4	4	4	7	4	9	32
Group II	5	13	6	8	9	11	52
Before sulfanilamide .	3	4	5	4	5	7	29
After sulfanilamide .	1	4	1	5	7	13	31
On discharge:							
Group I	1	1	4	5	5	15	31
Group II	2	4	7	10	5	19	47
Six months later:							
Group I	0	0	1	1	3	7	12
Group II	0	0	0	5	7	6	18

The phenolsulphonephthalein test showed the kidney function to be less impaired at all times than did the urea clearance (Fig. 4). On admission, 56% of the patients in Group I and 28% of the ones in Group II excreted more than 70% of the dye in 2 hours. At

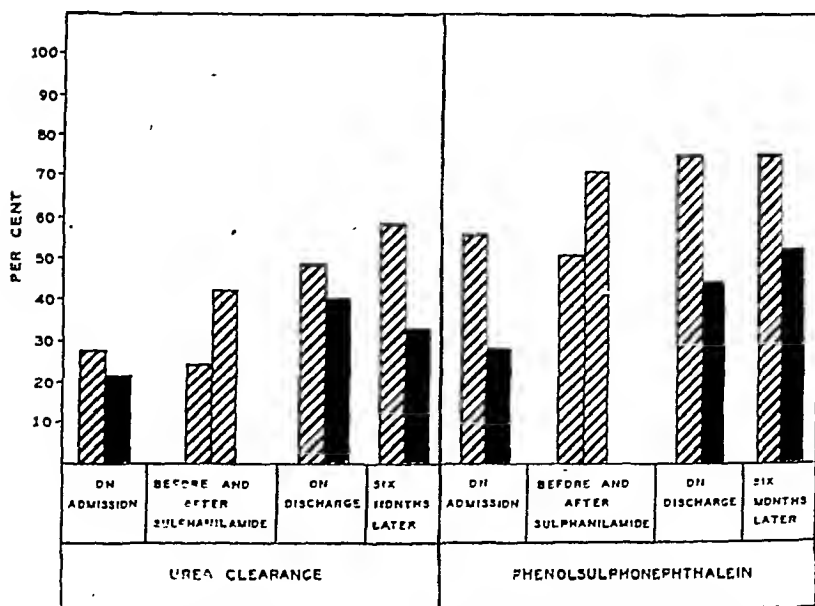


FIG. 4.—Percentage of patients with urea clearance greater than 75% of normal or phenolsulphonephthalein excretion greater than 70% in 2 hours.

discharge, there were 75% in Group I and 44% in Group II that excreted this quantity of dye. Examination of some of these patients 6 months later showed this percentage to be 75 in Group I and 52 in Group II. Before sulfanilamide was started, 51% of the subjects in Group I had a function above 70% and at the conclusion of this therapy there were 71%. In only 1 case did this test show the function to be lower at the end of treatment than at the beginning.

DURATION OF EDEMA AND HYPERTENSION. The edema was found to be of shorter duration in the subjects treated with sulfanilamide than in those not receiving this drug. In the former group it averaged 16 days, though varying from 2 to 135 days, while in the latter group it averaged 20 days with a variation of from 2 to 95 days. There was no demonstrable edema at any time in 7 subjects in Group I and in 9 subjects in Group II.

It was observed that in most instances, in each group, the disappearance of the edema was associated with a disappearance of the hypertension and, as was the case with the edema, the hypertension was of shorter duration in the group treated with sulfanilamide than in the control group, averaging 15.8 days in the former, with a variation of from 2 to 40 days, as compared with an average of 25 days and a variation of from 3 to 95 days. There were 13 in Group I who never exhibited any hypertension. In 1 instance the elevation of blood pressure persisted for 3 months (this patient is not included in the above average). At discharge and 6 months later, only 1 of the patients in Group I had hypertension. There were 14 subjects in Group II who never exhibited any hypertension and there were 7 who maintained an elevation in their blood pressure throughout their stay in the hospital. Six months later 4 of these continued to have this elevation whereas in 2 it had disappeared. The other patient did not return for examination.

CLINICAL OUTCOME. In attempting to evaluate the final outcome in these two groups of nephritis, it is desirable to consider first the number of deaths that occurred in the acute phase of the illness. During this stage, there are usually several factors that play a part in the fatal termination. In many patients the severity of the infection itself is of paramount importance; in some acute myocardial failure leads to a fatal termination; and in others symptoms of uremia are predominant, while in most instances acute anuria is present before death.²³

It is apparent, therefore, that control of the acute infection and relief of the acute myocardial failure, if successful, may save the life of the patient.

It has appeared to us that the employment of sulfanilamide and the use of digitalis may have had this result in a few of the patients in Group I (Fig. 5). There was only 1 death in this group of 42 patients during the acute phase of the disease. This occurred in a

man 63 years of age with a deep infection of the thigh, not proven to be caused by hemolytic streptococci. In Group II there were 12 deaths (11%) during the acute phase. Five patients had severe hemolytic streptococcic infections of the throat accompanied in 1 by suppurative cervical lymph adenitis and complicated in all by pneumonia. One patient died in uremia with acute infection of the facial sinuses due to beta hemolytic streptococci. In 2 patients the acute nephritis followed scarlet fever, with complicating hemolytic streptococcic infections of the throat and ears during which time death resulted from uremia with myocardial failure. One patient died of pneumonia and pericarditis, 1 of acute streptococcic infection of the throat complicated by measles and hyperthyroidism, 1 from uremia and myocardial failure associated with a hemolytic streptococcic infection of the throat complicating sickle-cell anemia, and 1 from acute cardiac failure and nodal rhythm.

It is not inconceivable that if the newer chemotherapeutic measures had been available when these patients came under observation, the lives of some of them might have been saved.

These deaths account in part for the comparatively low recovery rate in the control group; but they are not entirely responsible since the beneficial effect of sulfanilamide is manifested not only by the distinctly lower death rate during the acute phase, but also in modifying the subsequent course of the disease.

Though it is admittedly difficult to determine accurately when complete healing of the nephritis has taken place, we have established the following criteria as being satisfactory for this purpose: The concentrated specimen of urine must be free from albumin, red blood cells and casts on more than one examination, often several, made at different intervals; or the Addis count must be within normal limits; the blood pressure must be within normal limits, and the urea clearance and phthalein excretion normal. Many of the patients whom we have considered as cured have been submitted to these tests on several occasions without showing abnormalities. A few patients have shown normal Addis counts when resting quietly in bed, but have voided urine when up and about that contained traces of albumin and small numbers of red blood cells. These patients have been classed as individuals in the latent stage of the disease.

Using these criteria for the basis of classification, 29 (74.3%) of the total number of 39 patients treated with sulfanilamide who have been followed for at least 2 years are well, whereas only 56 (52%) of the 108 control patients followed for at least the same period of time have recovered (Table 4). In Group I there are 7 patients (16.6%) of the total number of 42 who are now in the quiescent stage. Three of these have been observed for only a few weeks so that the final outcome cannot be determined. Two of these have improved rapidly, 1 has done poorly. Two of the

39 patients in Group I are, after 2 years, progressive. None has died in the chronic stage of the disease.

In the control group, 11 patients (10% of the entire 108) are in the quiescent stage and 29 (27%) have progressed to a chronic stage, from which 5 of these 29 individuals have died.

TABLE 4.—CLINICAL OUTCOME OF PATIENTS FOLLOWED FOR 2 YEARS OR LONGER.

	Group I.		Group II.	
	No.	%.	No.	%.
Well	29	74.4	56	52.0
Latent	7	18.0	11	10.1
Progressive	2	5.0	24	22.2
Dead	1	2.6	17	15.7
Total	39	100.0	108	100.0

Discussion. On the basis of the foregoing facts, it seems reasonable to conclude that in most respects the 42 patients receiving sulfanilamide have shown more rapid improvement than the 108 control individuals observed for a similar length of time. This has occurred in spite of the fact that in the two groups there has been relatively little difference as regards the type or severity of the initial infection, the interval from the infection to the onset of the nephritis, the type or the severity of the nephritis, or the interval from the onset of the nephritis to the admission of the patient to the hospital. Furthermore, other forms of treatment have been essentially the same in each group. In association with the use of sulfanilamide there has occurred, in most instances, a great reduction in the number of beta hemolytic streptococci in the throat or other foci of infection. This antibacterial effect apparently did not interfere with the immunologic response, as exhibited by the antistreptolysin titer of the blood serum, inasmuch as the quantitative changes in the serum bore the same relationship to the course of the disease in Group I as in the controls. The albumin and formed elements disappeared from the urine faster in the former groups; the kidney function, as indicated by the urea clearance and phenolsulphonephthalein tests, exhibited a definitely greater improvement; and the edema and hypertension were of shorter duration. Finally, of greatest importance was the fact that the incidence of recoveries was greater and the number of patients pursuing a progressive course distinctly less in the group that received sulfanilamide therapy.

Contrary to our expectations, we were not successful in rendering the tonsils free of beta hemolytic streptococci in more than one-half the cases. We can reconcile this with the clinical improvement, and the smaller number of exacerbations in the nephritis following tonsillectomy, only by assuming that the sulfanilamide had exerted in the tonsils its usual rôle of bacteriostasis.

To state precisely the mechanism by which sulfanilamide has

effected an improvement in the inflammatory reaction in the kidney is not possible, inasmuch as the etiology of acute hemorrhagic nephritis has not been proved. Since there is very good presumptive evidence, however, to show that acute nephritis is associated with hemolytic streptococcic infections (usually in the upper respiratory tract), since sulfanilamide has proved to be a potent defense against this organism regardless of where the infection lies, and since it is

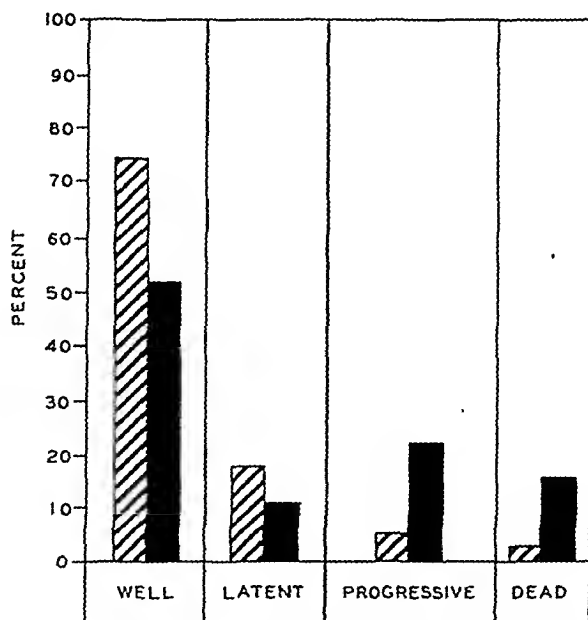


FIG. 5.—Clinical outcome of patients followed for 2 years or longer.

believed that the disappearance of infection and of this organism was related to recovery, there is reason to suppose that the beneficial effect of sulfanilamide resides in its antibacterial action on the infection.

Frequent urinalyses and kidney function tests failed to demonstrate that sulfanilamide had caused any renal damage either in these or in other patients. This is true in spite of the fact that most patients had edema, hypertension, large quantities of albumin with formed elements in the urine, and an elevation of the non-protein nitrogen of the blood at the time that chemotherapy was started.

Sulfanilamide should be given for several days preceding and following tonsillectomy. It is useful to follow the same principle in association with other surgical procedures.

Owing to the fact that it was desirable to employ sulfanilamide with some caution in these patients many of them were not treated

with entire satisfaction. The drug was usually stopped when fever or nausea developed, and it now appears that the amounts of sulfanilamide employed were sometimes unnecessarily large. Frequently, again, the drug was not given over a sufficiently long period in small doses of 1.5 to 3 gm. a day. It may well be desirable to institute during the period of convalescence a form of therapy similar to that devised by Thomas and France²¹ and by Coburn and Moore^{1a,b} in their effort to prevent recurrences of rheumatic fever. In their hands the method has been highly successful and promises to be of signal value in the prophylactic treatment of rheumatic fever. It is our intention to adopt this procedure and to administer doses of sulfanilamide varying from 1.5 to 3 gm. a day over long periods of time following recovery from the acute phase of the disease, or possibly until all evidence of disease of the kidney disappears. It is hoped that by this means the duration of the disease may be shortened, recrudescences of hemolytic streptococcal infection prevented and the number of final recoveries increased.

Conclusions. A comparative study has been made of the course of acute hemorrhagic nephritis in a group of 42 individuals treated in essentially the same manner as a group of 108 similar individuals, except that in the former group sulfanilamide was administered. Most of these patients have been followed from 2 to 5 years or longer.

The results indicate that in the subjects receiving sulfanilamide the foci of infection have cleared up more rapidly, the signs of renal damage have disappeared more rapidly, the exacerbations of the nephritis following tonsillectomy have occurred less frequently, the duration of the edema and hypertension have been shorter and the clinical recoveries have been greater.

In the group of 42 patients treated with sulfanilamide there was 1 death in the acute stage. Complete recovery occurred in 15 of 33 cases who returned for observation after 6 months and in 29 of the 39 patients, or in 74.3% of those followed for at least 2 years. Three additional patients who have been followed for only a few weeks are in a quiescent stage. Five of the 39 patients are in the quiescent stage, and 2 are in a progressive stage.

In the control group of 108 patients, on the other hand, there were 12 deaths in the acute stage, and 5 deaths following a progression to chronic nephritis. Of the entire group of 108 patients there are only 56 complete recoveries, giving a percentage of 52; 11 patients are in the quiescent stage, and 24 in the chronic progressive stage of the disease.

The course of the immunologic reactions as exemplified by the antistreptolysin titer of the blood serum has been practically the same in both groups.

There was no evidence that sulfanilamide caused renal damage in any case.

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THE EFFECT OF VARIOUS SULFONAMIDES ON HEMOLYTIC STAPHYLOCOCCUS MEASURED WITH THE MANOMETRIC TECHNIQUE.

BY WALTER KEMPNER, M.D.,

ASSISTANT PROFESSOR IN MEDICINE, DUKE UNIVERSITY SCHOOL OF MEDICINE,

C. SCHLAYER, PH.D.,

RESEARCH ASSISTANT, DEPARTMENT OF MEDICINE, DUKE UNIVERSITY SCHOOL OF MEDICINE,

AND

PERCY SUMMERS, M.D.,

ROCKEFELLER FELLOW IN MEDICINE FROM THE MEDICAL SCHOOL OF THE UNIVERSITY OF LIMA, PERU,
DURHAM, N. C.

In previous papers on the effect of various sulfonamides on the growth rate of *Brucella melitensis* and of pneumococcus,^{1,2} we discussed the advantages of the manometric technique of measuring the bacterial metabolism quantitatively under physiologic conditions, as compared with the conventional bacteriologic methods of culturing and counting the bacteria. In this paper we are reporting the results of manometric determinations of sulfonamide effects upon the growth rate of staphylococcus.

Experimental. Very young cultures of three strains of hemolytic *Staphylococcus albus* and *aureus* were examined. They were isolated from the blood of a staphylococcus endocarditis, from the pus of a diabetic patient

with furunculosis and from a conjunctivitis exudate. Beef infusion-0.5% glucose-1% Difco-Bacto-peptone broth (pH 7.4) was used as culture medium. Rough differences in the number of bacteria were measured with the photorefractometer (Libby). The bacteria volume was determined in the hematocrit by centrifuging aliquot parts of the bacterial suspension.

Since measuring the number and volume of the bacteria with the photorefractometer and the hematocrit gives no information about the activity of the bacteria, the metabolism of the staphylococcus culture to be used was measured in a preliminary manometric experiment. In this, the oxygen consumption of one or two colonies of a 10- to 24-hour-old blood agar culture suspended in glucose-peptone broth was recorded (1 to 3 hours) until active growth was quantitatively established. These cultures of definite age and activity were used for making the suspensions for the final experiments with the sulfonamides.

Conical manometer vessels of 18 to 20 cc. capacity contained 2 cc. of the bacteria suspension in the main space. In the aerobic experiments the side bulbs of the manometer vessels contained 0.2 cc. 20% NaOH, and the oxygen consumption of the cultures was measured either in air or in other O_2/N_2 mixtures. In the anaerobic experiments the medium was buffered with 0.01 to 0.025 M sodium bicarbonate and the CO_2 formation was measured at various CO_2 concentrations in nitrogen. The temperature was 38° C.

The drugs tested were sulfapyridine sodium (sodium 2-sulfanilyl amino-pyridine monohydrate, Merck), sulfaguanidine (sulfanilyl guanidine, Lederle), sodium disulon (sodium sulfanilyl sulfanilamide, Alba Pharmaceutical Co.), sulfadiazine (2-sulfanilamido-pyrimidine, Lederle), sulfathiazol (2-sulfanilamido-thiazol, Winthrop), and sulfathiazol sodium (sodium 2-sulfanilyl-aminothiazol sesquihydrate, Squibb). In testing the potency of the various drugs one should avoid using relatively small quantities of bacteria with relatively high concentrations of drugs, and low concentrations of the drugs with large quantities of bacteria, since in the first instance the same strong inhibitory effect is seen no matter what drug is used, and in the second, no inhibitory effect can be seen at all. One must therefore vary drug concentration and bacteria inoculum until maximal discrepancies in the effectiveness of the various drugs in equal or different concentrations become apparent.

Figure 1 shows a typical experiment that complies with these conditions. The potency of the various drugs can be read from the figures obtained for the oxygen consumption of a staphylococcus culture, recorded every 15 minutes. The percentage concentration of the various drugs used was 0.5 mg. per 100 cc. The initial density of the suspension was 700,000 organisms per cc. The original culture was 1 hour old. The least effective of the drugs tested was sulfaguanidine. After 4½ hours the oxygen consumption was 665 c.mm. per hour as compared to 865 c.mm. of the drug-free control. Next in potency was sulfapyridine sodium (623 c.mm. O_2 consumption per hour), then sodium disulon (534 c.mm.), and sulfadiazine (402 c.mm.). The most effective was sulfathiazol sodium and sulfathiazol (182 and 203 c.mm.). The number of bacteria

grown, even after so short a period, was in sulfadiazine more than twice, and in sulfapyridine sodium more than three times the growth in sulfathiazol.

It is worth emphasizing that in the three strains of staphylococcus tested, sulfadiazine had a greater growth-inhibiting effect than sulfapyridine sodium, whereas in the case of pneumococcus (Types I, II, III), examined under the same experimental conditions, sulfapyridine sodium proved definitely superior to sulfadiazine. For both bacteria, sulfathiazol was the most potent growth inhibitor.

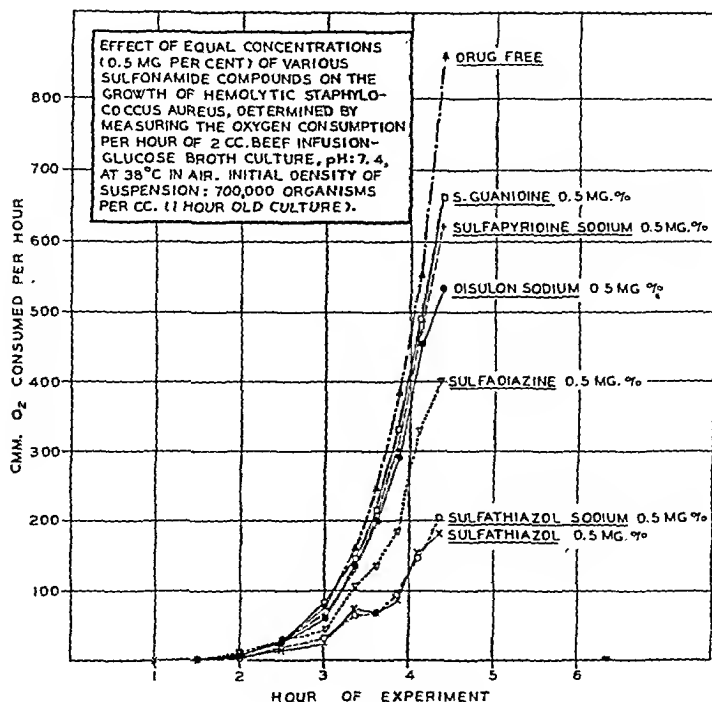


FIG. 1.

Figure 2 shows the effect of 0.5 mg. per 100 cc. and 1 mg. per 100 cc. sulfadiazine and sulfathiazol on the staphylococcus growth rate. After $4\frac{1}{2}$ hours the growth inhibition of 0.5 mg. per 100 cc. sulfadiazine was 61% and of 1 mg. per 100 cc. sulfadiazine 77%, whereas 0.5 mg. per 100 cc. and 1 mg. per 100 cc. sulfathiazol caused inhibitions of 83% and 84% respectively.

It seemed worthwhile to establish whether the growth-checking effect of the sulfonamides depends on an optimal oxygen concentration, like that of atmospheric air, or whether it can also be demonstrated at lowered oxygen concentrations and under anaërobic conditions. Figure 3 shows the effect of 3.3 mg. per 100 cc. sulfa-

thiazol on the staphylococcus growth rate in a beef-infusion-glucose-broth culture ($2.35 \cdot 10^{-2}M$ $NaHCO_3$), determined by measuring the CO_2 formation at 5% CO_2/N_2 (pH 7.44). The initial density of the suspension was about 50 times as high as that in the foregoing experiments (37 million organisms per cubic centimeter). The original culture used as inoculum was 1 hour old. After an experimental

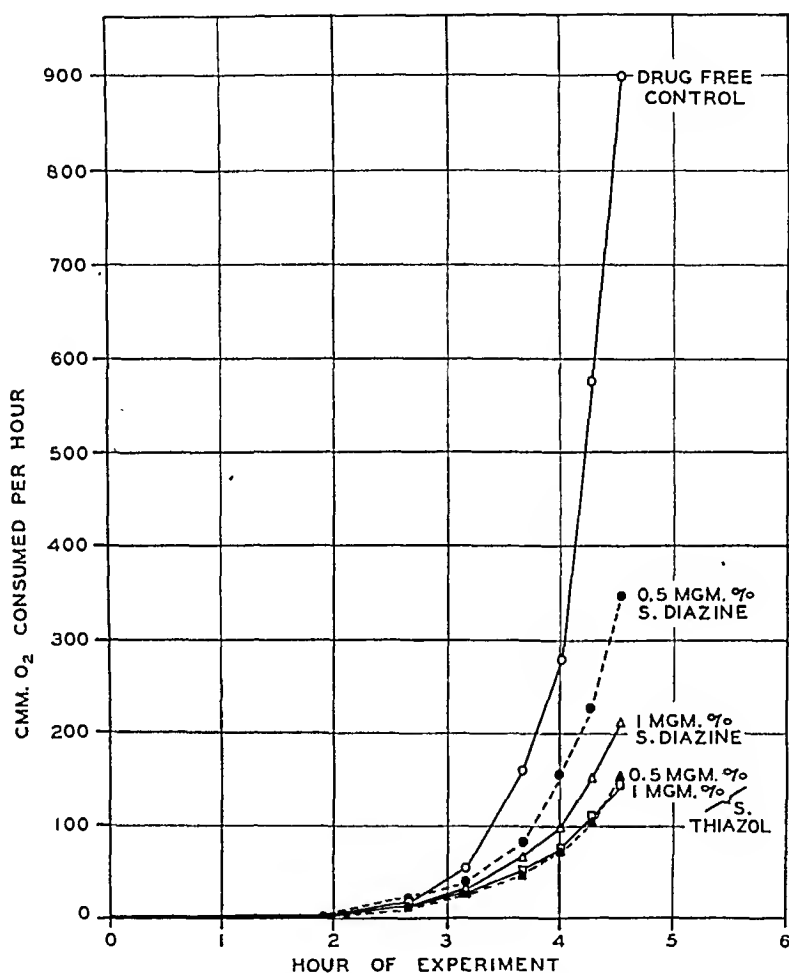


FIG. 2.—Effect of 0.5 mg. % and 1 mg. % concentrations of sulfadiazine and sulfathiazol on growth rate of hemolytic staphylococcus. Initial density of suspension: 740,000 organisms per cc. (1 hour old culture).

period of 3 hours, the drug-free control showed a growth of bacteria corresponding to a CO_2 formation of 264 c.mm. per hour, whereas the CO_2 formation in the sulfathiazol containing culture was only 52.5 c.mm. Under anaërobic conditions then, in spite of the large inoculum, a concentration of 3.3 mg. per 100 cc. sulfathiazol caused a growth inhibition of 80%. Sulfadiazine, sulfaguanidine and sulfapyridine sodium too exhibited a strong inhibitory effect on the

growth rate of staphylococcus under anaërobic conditions. In O_2 concentrations of 8 vol. % and 4 vol. % the inhibitory effect of the sulfonamides was likewise apparent.

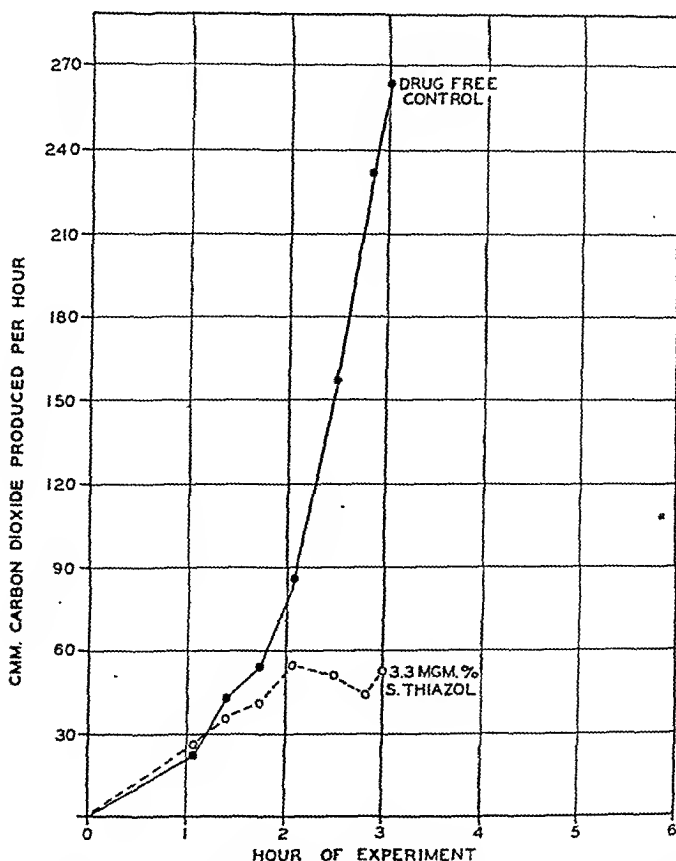


FIG. 3.—Effect of 3.3 mg. % sulfathiazol on growth rate of hemolytic staphylococcus in the absence of oxygen.

Summary. The effect of various sulfonamides on the growth rate of 3 pathogenic strains of hemolytic staphylococcus was determined by measuring manometrically the oxygen consumption and anaërobic CO_2 formation of glucose-peptone-broth cultures. The order of potency of the various drugs tested was as follows: least effective, sulfaguanidine with a bacteria growth after $4\frac{1}{2}$ hours which corresponded to an oxygen consumption of 665 c.mm. per hour, as compared to 865 c.mm. of the drug-free control; then sulfapyridine sodium with 623 c.mm.; sodium disulon with 534 c.mm.; sulfadiazine with 402 c.mm.; and sulfathiazol and sulfathiazol sodium with 203 and 182 c.mm. respectively.

The amount of *staphylococcal* growth in sulfapyridine sodium was more than 200% in excess of that in sulfathiazol, while that in

sulfadiazine was only 100%. In *pneumococcus* cultures, examined under the same experimental conditions, sulfapyridine sodium was definitely superior to sulfa diazine. For both bacteria sulfathiazol was the most potent inhibitor.

By varying the concentrations of the drugs it could be shown that sulfadiazine was only half as effective as sulfathiazol as a growth inhibitor of staphylococcus. The sulfonamides inhibit the staphylococcus growth rate not only at optimal, but also at lowered oxygen concentrations, and under anaërobic conditions.

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CAVITY HEALING AND BRONCHIAL OCCLUSION.*

BY WALTER PAGEL, M.D.,

ACTING PATHOLOGIST,

AND

F. A. H. SIMMONDS, M.D.,

MEDICAL SUPERINTENDENT.

LONDON, ENGLAND.

(From the Pathology Department, Central Middlesex County Hospital, London, and the Middlesex County Sanatorium, Clare Hall, Barnet, England.)

THE anatomy of healed cavities which up to a short time ago was a matter of conjecture can now be based on reliable observations followed up by Roentgen ray studies and necropsy. The number of such cases, however, is still small and there is much speculation as to the complicated series of events leading to closure or elimination of cavities. Three anatomic forms of healed cavities can be differentiated: 1, The solid focus due to retention, inspissation and final calcification of the cavity contents; 2, the radiating scar; 3, the bronchiectatic area remaining after the substitution of caseous and tuberculous elements in the cavity wall by ordinary granulation tissue, with subsequent epithelialization and fibrous shrinking of the space.

No figures are available assessing how often one or the other type of change occurs in cavity healing. All this justifies adding to our previous report (Pagel and Simmonds¹²) a further series illustrating the anatomy and development of cavity healing.

Case Reports. CASE 1.—R. R., female, aged 14, had cough for 1 year with sputum positive for tubercle bacilli, and advanced tuberculosis in each lung with cavities (probably 3 or 4 in the left lung) each of approximately 1 to 1½ inches in diameter. Patient was treated by strict rest for 4 months,

* Owing to postal difficulties, proof of this article was not returned to the author for correction.

then left artificial pneumothorax (Dec. 9, 1938) and right artificial pneumothorax (Dec. 28, 1938) in view of grave prognosis. Cavities still present on Jan. 1, 1939. Died, Feb. 6, 1939.

Necropsy revealed in the subpleural ventro-axillary aspect of the left upper lobe, 3 soft caseous but solid foci with a fibrotic capsule, 0.2 cm. thick. Two were in the subapical and infraclavicular region and one in the lower parts of the upper lobe near the interlobar fissure. This focus was larger than the others. Its largest part belonged to the dorsal portions of the lobe. In the ventral parts it forked and was seen in a section as two partly separated foci. Its contents were softer than those of the apical foci, consisting of caseous, necrotic, partly edematous material rich in leukocytes, poor in tubercle bacilli, and lacking collagenous and elastic elements. Similar material was found in the large bronchi leading to the focus. In the formalin specimen it tended to retract from the periphery. The lung tissue surrounding the apical and subapical foci was aerated and slightly emphysematous, whereas the dorsal parts of the lower and largest focus were in collapsed and indurated lung parenchyma.

Obviously the solid foci correspond in size and situation to the three cavities seen in the roentgenograms. *The cavities were, therefore, converted into solid foci.* The last roentgenogram was taken 4 weeks before death. This case thus affords an opportunity of estimating the *minimum time necessary for the disappearance of a cavity.* It should be noted that the cavities brought to closure were of considerable size, the lowest one reaching a diameter of about $1\frac{1}{2}$ inches.

CASE 2.—N. Q., female, aged 17, had tuberculosis for 1 year, with right artificial pneumothorax in June, 1937, for hemoptysis. A cavity was present in right lower zone, and had spread on left side in 1938. Patient died following spontaneous pneumothorax on left side (Dec. 9, 1938).

A cavity in the right lower lobe (Figs. 1 and 2) disappeared between the roentgenograms of Dec. 10, 1937, and May 26, 1938; it was much smaller in the roentgenograms of July 6 and Sept. 13, 1937 (in spite of neighboring infiltration). It was still smaller in the roentgenogram of Oct. 18, 1937 (after absorption of neighboring infiltration).

Necropsy. In the dorsal portions of the right lower lobe, lung tissue was collapsed and indurated and contained an old caseous encapsulated focus the size of a bean (Fig. 3). Several similar but smaller nodules were found, one in the apex and another in the more caudal parts of the lower lobe. In addition, a complete and calcified primary complex was detected in the right lower lobe and corresponding hilar gland. No cavity was visible in the right lung.

The area of induration containing an old caseous encapsulated focus in the right lower lobe obviously corresponds to the cavity followed up in the roentgenograms until disappearance. According to radiologic evidence the conversion of the cavity into a solid focus was achieved in less than 5 months. It was a fairly large and not a thin-walled cavity and had been greatly reduced in size 2 months after pneumothorax was induced.

CASE 3.—M. B. W., female, aged 38, had bilateral pulmonary tuberculosis for 3 years, with cavity in right upper lobe, diameter $1\frac{1}{2}$ inches (Fig. 4). Sputum tubercle bacilli positive. Extrapleural pneumothorax in November, 1937. Cavity not seen thereafter (Fig. 5). Patient died, Jan. 21, 1940, following spontaneous pneumothorax on the left side.

Necropsy. The right upper lobe especially in the apical part was greatly shrunken, the pleura being about 1 cm. in thickness. The dorsal parts contained besides a subpleural emphysematous bulla and a few small scattered caseous nodules, an old caseous round focus with a thin capsule. The ventral parts of the caseous round focus connected with a bronchus filled

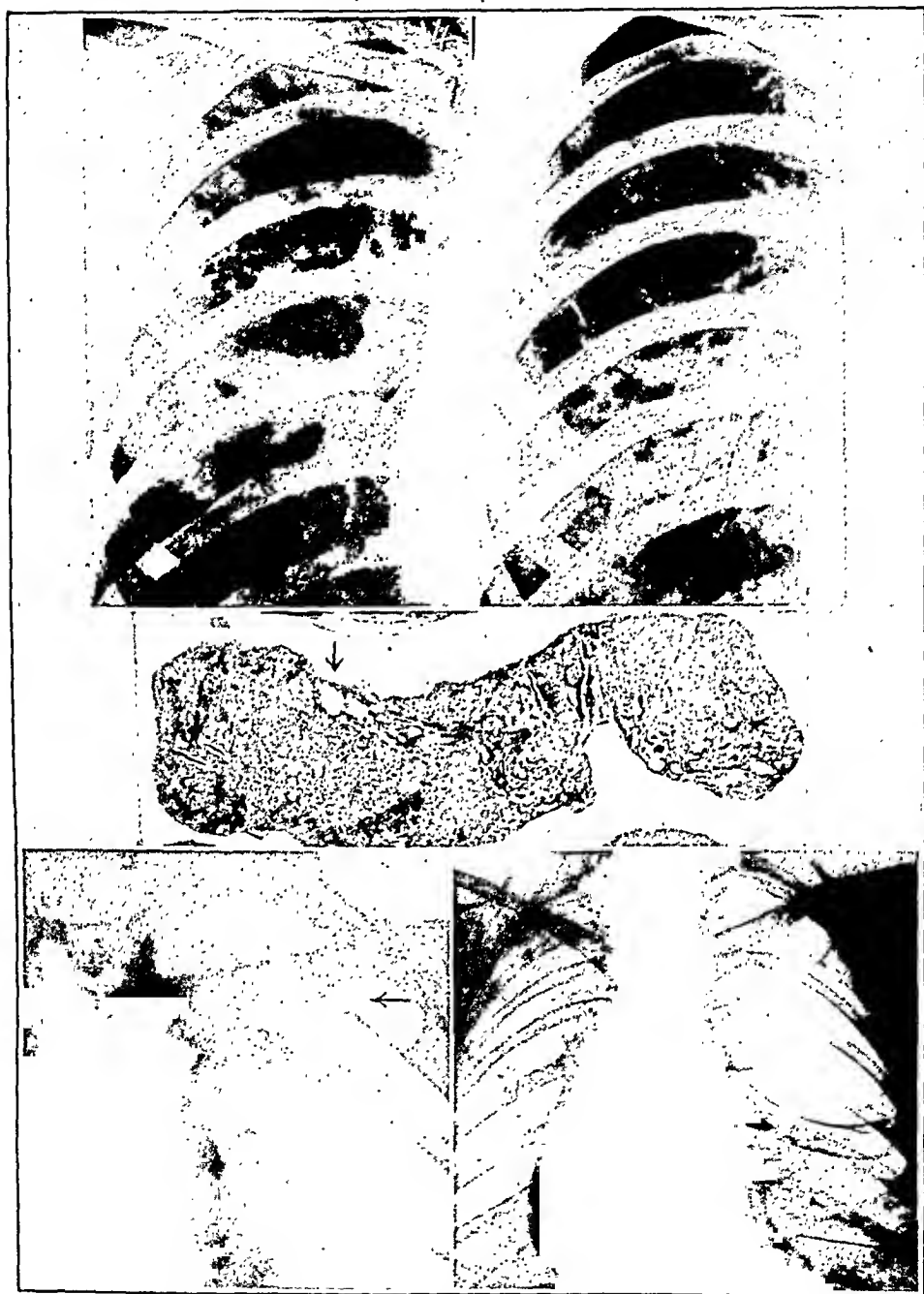


FIG. 1.—Case 2 (July 6, 1937). Right lung. Cavity in lower zone.

FIG. 2.—Case 2 (July 27, 1938). Cavity disappeared.

FIG. 3.—Case 2. Solid focus in lower part of right lower lobe corresponding to site of cavity. No cavity visible.

FIG. 4.—Case 3 (May 26, 1937). Large cavity in the infraclavicular part of the left upper lobe.

FIG. 5.—Case 3 (April 13, 1939). Extrapleural pneumothorax. Cavity disappeared.

with old caseous material and therefore very similar in nature to the round focus itself (Fig. 6). This area of caseous bronchitis was most impressive. The round focus and caseous bronchitis were obviously the remains of the cavity shown in the original roentgenogram and disappeared after extra-pleural pneumothorax treatment.

CASE 4.—B. M., male, aged 26, had tuberculosis involving both lungs for $2\frac{1}{2}$ years. In the right side, he had a large cavity below the clavicle ($2\frac{1}{2}$ inches in diameter), and on the left side, three cavities were present, each about 1 inch in diameter, one just below the clavicle and the others more caudally (Fig. 7). A left pneumothorax was induced (March 8, 1940), and the upper and lowest cavities were thereafter no longer visible, although the middle cavity persisted (Fig. 8). This cavity ruptured after the adhesion over it had been divided.

Necropsy. The subapical region of the left upper lobe contained an encapsulated caseous focus which was round in the dorsal parts and oblong in the more ventral aspects. The capsule was thin, 0.2 cm. in width, the surrounding lung tissue emphysematous and not collapsed or indurated. (a) The cavity which the roentgenogram showed in the infraclavicular parts of the left lung was obviously substituted by a solid round and partly oblong caseous focus. A tear into the middle part of the upper lobe (b) was present at the site of the central cavity (spontaneous pneumothorax). Another solid focus represented the lowest cavity (c) (Fig. 9).

CASE 5.—R. H., male, aged 23, had tuberculosis of left lung for 3 years with several cavities, and was treated by artificial pneumothorax and adhesion section (June, 1937). Spread of disease noted in right lung, so left artificial pneumothorax was abandoned in May, 1940, and right artificial pneumothorax begun. Death resulted from right spontaneous pneumothorax. Roentgenogram, May 18, 1938: Extensive cavitation left upper lobe, uncollapsed by pneumothorax. Roentgenogram, July 13, 1940: After artificial pneumothorax cavitation right upper lobe, no obvious cavity on left side.

Necropsy revealed a small shrunken cavity the size of an almond in the dorsal parts of the right upper lobe, near the interlobar fissure. The cavity was almost completely filled with inspissated contents, but still contained a small lumen which did not communicate with the bronchial system.

Left lung: The upper lobe contained three well-encapsulated round foci with adjacent caseous bronchitis and in addition a few smaller nodules, but there was no cavity visible. The lung, as a whole, was shrunken and the pleural membrane thickened.

The cavities visible in the roentgenogram in the left upper lobe were replaced by solid round foci, whereas there was still a remnant of the cavity in the right upper lobe. The cavity in this part, however, is considerably shrunken, almost filled with inspissated contents and does not communicate with the bronchi. It may be assumed that it would have closed completely if death had not intervened. The actual interval between the last roentgenogram showing a large uncollapsed cavity in the right lung and death was 3 weeks. Note that in this interval the cavity had nearly, though not completely, been replaced by a solid focus.

CASE 6.—Male, aged 41. Roentgenogram showed a cavity and infiltration in right mid-zone (Fig. 10). Artificial pneumothorax begun in December, 1936, was followed by adhesion-section, and maintained for 4 years. Roentgenogram in September, 1940, showed no lumen to an opacity representing previous cavity and infiltration (Fig. 11). Died April, 1941. At necropsy, in the right lower lobe there was an old dry caseous, partly calcifying, nodule about 1 inch in diameter, with adjacent caseous calcifying bronchitis (Fig. 12). No cavity was seen in the right lung.

FIG. 6.

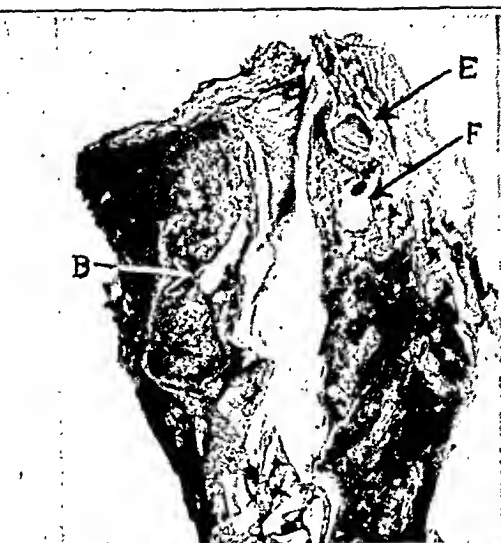


FIG. 7.



FIG. 8.



FIG. 9A.



FIG. 9B.



FIG. 6.—Case 3. Left upper lobe: *F*, Solid focus at the site of the cavity; *E*, emphysematous bulla; *B*, caseous bronchitis attached to focus.

FIG. 7.—Case 4 (Sept. 18, 1939). Left upper lobe showing three cavities (arrows).

FIG. 8.—Case 4 (June 21, 1940). Two cavities have disappeared; cavity in mid-zone persisting.

FIG. 9.—Case 4. Left upper lobe: (*a*) Solid oblong focus (caseous bronchitis) in the subapical parts corresponding to cavity shown in the infraclavicular area of Fig. 7; (*b*) slit-shaped collapsed cavity in mid-zone with perforation corresponding to mid-zone cavity in Fig. 8; (*c*) solid focus in lower part of left upper lobe corresponding to lower cavity in Fig. 7.

Discussion. All cases presented in this series are examples of cavity healing by conversion of the space into a solid, caseous and calcifying focus. At necropsy no cavity could be traced, but corresponding in situation, shape and size in the specimen was a caseous nodule looking like an ordinary "round focus."

FIG. 10

FIG. 11

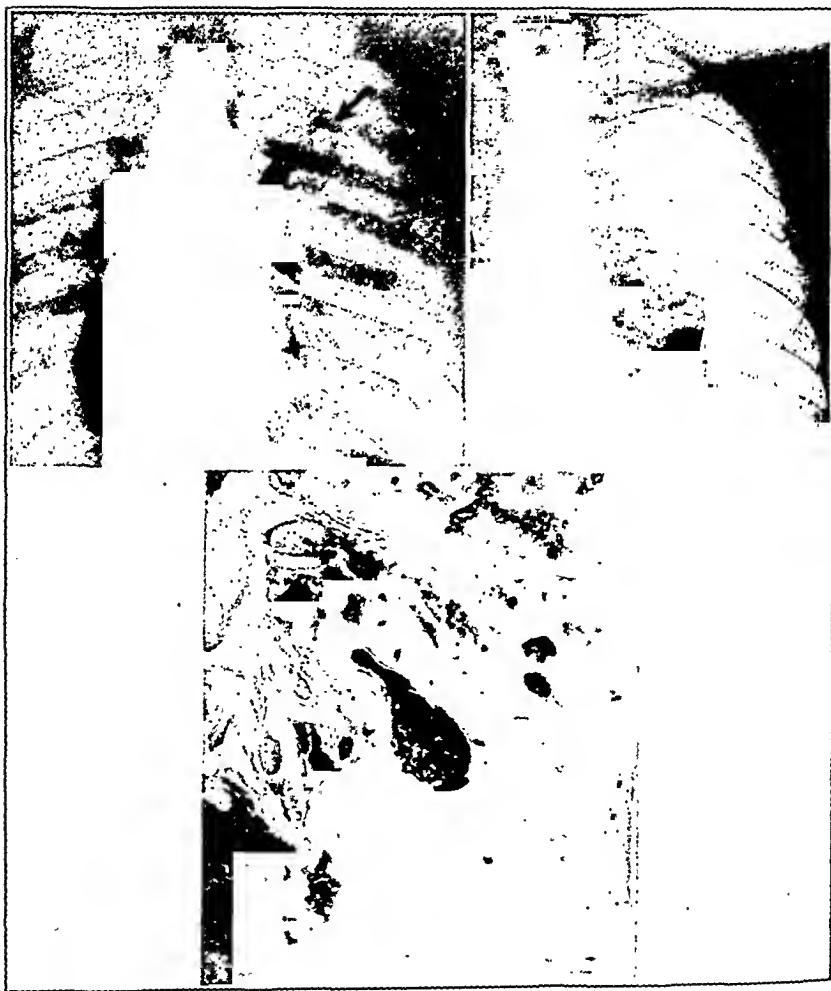


FIG. 12

FIG. 10.—Case 6. Oct. 17, 1936. Cavity (arrow) and infiltration in the right mid-zone

FIG. 11.—Case 6. Sept. 17, 1940. Large artificial pneumothorax right. Cavity replaced by solid shadow (?scar).

FIG. 12.—Case 6. Anatomic specimen of lower part of right upper lobe showing calcifying round focus with *caseous bronchitis* at site of cavity.

Various stages of the development are represented in the cases described. The last stage, *i. e.*, calcification, was traced through from the initial cavity in our observation reported in a previous paper (Pagel and Simmonds¹²).

In the present case, Case 1, the process of closure must have been very recent. The roentgenogram still showed the cavities, but at necropsy, foci consisting of a soft caseous matter had taken their place. Two points are noteworthy in connection with this case: (a) The short interval of 4 weeks necessary for the conversion. In our previous series¹² (*loc. cit.*, 1939, Case 4) a similar instance was reported and an interval of 2 months was found between the last roentgenogram still showing the ring shadows of cavities and the necropsy revealing soft, but solid nodules. Three months was the interval in the observation by Pagel and Roberts.¹⁰ We are in accord with Pinner^{14b} that the soft focus as seen in these cases may revert, and need not necessarily result in permanent closure, but it is, no doubt, an earlier stage of the older caseous and calcifying nodule which is found in securely stabilized, *i. e.*, healed cavities. (b) The same soft material as in the nodule was found in the bronchi leading to the closed cavities. One of them consisted in its whole ventral part of a system of bronchi with caseous material ("caseous bronchitis"). This shows the importance of the bronchi at an early stage in cavity healing. Even more pronounced was the caseous bronchitis in Case 3 which showed a more advanced stage with beginning calcification of the closed cavity.

The same prominence of caseous bronchitis attached to closing or healed cavities has been noted in our previous series¹² (*loc. cit.*, 1939, Cases 2 and 3) and it appears to be an essential feature. Only in the present Case 2, we found no caseous bronchitis, the bronchi leading to the closed cavity being obliterated, ending blindly in the fibrotic capsule.

Such frequent observation of an area of caseous bronchitis immediately connected with the closing or healed cavity has not been recorded in the few anatomic cases of closed cavity healing which have been described, although it has been emphasized that there was no communication of the focus with the main bronchi (Wurm,¹⁶ Auerbach and Green³). Our findings are, however, important in the light of Coryllos' theory which regards early bronchial closure as the main factor in cavity healing. Pinner^{14b} has also recently given a qualified support to his view. The pictures presented in this paper are evidence in favor of this theory. It cannot be assumed that the bronchial changes are secondary to cavity closure for the following reason: If early infiltrations of the Assman type or early "round foci" are examined anatomically caseous bronchitis will be found connected with the focus in practically all cases, and in some of them forms the main part of the changes or the lesion

itself. If cavity formation occurs, liquefaction manifests itself first and most intensely in the focus and secondarily, to a lesser degree, in the caseous bronchus leading to it. This is probably due to multiplication of tubercle bacilli in the focus and not in the bronchus. It is obvious that after liquefaction of the central focus the bronchus often retains a considerable quantity of caseous material leading (particularly after induction of collapse therapy) to occlusion and kinking of its lumen with all consequences of cavity collapse, retention of cavity contents and healing, such as visualized by Coryllos. Thickening of the bronchial wall by tuberculous infiltration and edema increase the tendency to occlusion.

As a rule, caseous bronchitis which may thus lead to occlusion of the cavity is a diffuse lesion involving the bronchial wall in its whole length and not only a localized "bronchial plug" formed at the entrance of the bronchus into the cavity. Those authors who advocated the theory of cavity healing by bronchial occlusion suggested that a "bronchial plug" is responsible. Such "bronchial plugs" *do* occur. First anatomical evidence of this has been given by one of us (Pagel and Roberts¹⁰) in a case in which a "bronchial plug" accounted for distention and subsequent extensive collapse of a cavity and surrounding lung tissue.

These changes in the bronchi, beneficial when they lead to cavity healing, may be a most dangerous element in other cases when the bronchial lumen is partially obstructed and acts as a valve allowing air to enter, but not to leave the cavity. Such action leads to cavity distention, at times of severe degree. A liberal oxygen supply thus provided might accelerate the multiplication of tubercle bacilli and the breakdown of lung tissue. This, combined with intracavitary tension, leads to rupture and pleural contamination. It is shown by one of the cavities observed by Pagel and Roberts¹⁰ which exhibited extensive caseous changes all along the wall of the draining bronchus and had ruptured in the course of artificial pneumothorax treatment and adhesion cutting. In this way serous effusion and empyema are produced. This complication is much more common when the cavity fails to close by pneumothorax therapy—in other words, when the cavity remains tense by the valvular action outlined.

In our view, the presence of tuberculous caseous bronchitis connected with a cavity has not been sufficiently emphasized. Not only in the stages of cavity healing described or in the gross complications mentioned above, but at all stages of cavity formation and development, does this bronchial lesion play its part. Particularly in the earlier and elastic stages of the cavity, bronchial tuberculosis with its valve mechanism causes the increase, and sometimes rapid variation, in cavity size. It accounts for the circular shape of cavities seen in the Roentgen ray film, though such cavities seen

in the cadaver may be irregular in shape due to postmortem diffusion of the air in them.

As to the question of frequency of the various forms of anatomic cavity healing, the present authors have now collected a total of 10 cases. In only 2 of them "open cavity healing" (*i. e.*, healing of the cavity wall with persistence of the hole) was observed, while 8 were examples of cavity closure by conversion into a caseous or calcifying nodule. There was, however, no example of healing by formation of a radiating fibrotic scar.* Although the number of cases is still small and hardly permits of a statistical analysis, healing by conversion of the cavity into a solid focus seems to be the most frequent anatomic basis of cavity healing.

TABLE 1.—TYPES OF CAVITY HEALING IN CASES WITH NECROPSY.

Authors.	Open cavity healing.	Radiating scar.	Conversion into solid focus.	Hydrops of cavity.
Gilbert ⁵	..	1	1	
Page ⁹	1			
Alexander ¹	1			
Graeff ⁶	1	
McPhedran and Long ⁸	..	1		
Sweany ¹⁵	..	1		
Amberson ²	1
Page and Robinson ¹¹	1			
v. Karwowski ⁷	..	1		
Pinner ^{14a}	..	2		
Pinner ^{14b}	1	1		
Derscheid and Toussaint ⁴	1	
Page and Roberts ¹⁰	1	
Wurm ¹⁶	..	3	1	
Page and Simmonds ¹²	2	
Auerbach and Green ³	1	1	3	
Page and Simmonds	6	
Total	5	11	16	1

Total of 33 cases.

The same conclusion emerges from a study of the literature (Table 1) and has been drawn by Auerbach and Green.³ The frequency of cavity healing by conversion into a solid focus vindicates the assumption made by many clinicians for a long time that a calcified nodule often represents the last remnant of a healed cavity. This was often doubted and the calcified nodule regarded as ancient

* The 2 cases of open cavity healing are those described by Page⁹ and Page and Robinson,¹¹ the others observed by Page and Simmonds.¹² Page and Simmonds' paper had been sent to press for a long time when the observations by Wurm¹⁶ and Derscheid and Toussaint⁴ appeared. Before this there was only one observation of cavity healing by conversion into a solid focus, that by Graeff.⁶ The instance described by Amberson² shows a special form of cavity closure. It appears to be filled with a fluid rich in cholesterol crystals: "Hydrops of the Cavity." This may constitute an early stage of conversion into a solid focus, but in Amberson's case the hydrops had persisted for 10 years and it is unlikely that conversion would have occurred thereafter.

primary or postprimary foci appearing in the roentgenogram after the cavity has disappeared (Wurm¹⁶).

In the whole material of the present authors the healing of the cavity was spontaneous in only 1 case and in the other 10 collapse therapy had been employed (in 8 cases artificial pneumothorax, in 2 extrapleural pneumothorax).

Healing by conversion into a solid focus, as also that by formation of a radiating scar, obliterate the cavity; in open cavity healing a space persists. The first two methods of cavity closure may be grouped together, therefore, as far as the result is concerned. It is, however, doubtful whether they have anything else in common, notably in their pathogenesis. Nor is it conceivable that one form is the terminal phase of the other; in other words, solid caseous material which tends to calcification is unlikely to disappear completely and result in a fibrotic scar. It is more likely that either concentric fibrosis with a final scar, or inspissation of cavity contents without conspicuous fibrosis, occurs.

Why do some cavities heal by scar formation and others by conversion into a solid nodule? The answer to this question must remain a matter of speculation, but the following explanation is tentatively advanced. In our own series, pneumothorax was the means of therapy used. Following this operation there may be a rapid closure of the bronchus which has been already partially obstructed by caseation. The thick caseous lining of the cavity therefore does not have time to be discharged or to become absorbed, but absorption of the air in the cavity allows collapse and the caseous lining appears as a solid encapsulated focus. Where the bronchus is more patent, drainage is more free and there is less material to form a solid nodule. The closure of the cavity also may then be a slower process and be accomplished by concentric shrinking of the cavity wall by fibrosis and obliteration of the lumen with the final result of a scar.

In view of the rapid changes in size which cavities can assume (according to intracavitary pressure and the condition of the bronchi, as shown by the pioneer work of Pearson¹³) it is hardly justifiable to continue otiose considerations as to the maximum size of a cavity permitting of healing.

Summary. 1. A new series of 6 cases illustrating the anatomy of healed cavities is described.

2. All observations were examples of cavity healing by conversion of the space into a solid caseous nodule.

3. Four weeks appears to be the minimum time needed for this process.

4. Anatomic evidence was adduced that occlusion of the draining bronchi (either by obstructive caseous bronchitis or by formation of a caseous plug) is largely instrumental in this form of cavity healing.

5. Nine of 11 cases observed by the present authors and 16 out of 33 instances of anatomic cavity healing recorded in the literature, are examples of healing by conversion into a solid nodule. The frequency of this form vindicates the clinical assumption that not infrequently calcified nodules appear at the site of former cavities as the terminal stage of healing.

6. Conversion into a fibrotic radiating scar and into a solid focus differ in genesis and are identical only in the result—the disappearance of the actual space.

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HYPOPROTHROMBINEMIA IN PERNICIOUS ANEMIA.*

BY E. D. WARNER, M.D.,

ASSOCIATE PROFESSOR OF PATHOLOGY,

AND

C. A. OWEN, M.D.,

ASSISTANT IN PATHOLOGY,

IOWA CITY, IOWA.

(From the Department of Pathology, State University of Iowa.)

THE plasma prothrombin level is frequently 15% to 25% below normal in patients with chronic debility, despite administration of adequate amounts of vitamin K. This was found to be true of the nutritional deficiency states seen in the Nutrition Clinic of the Hillman Hospital at Birmingham, Ala. Similar values were obtained in many debilitated patients in the University Hospital at Iowa City. The combined results of both studies were recently reported.⁶ In contrast to this mild hypoprothrombinemia, several patients with pernicious anemia, seen at the Hillman Hospital

* Aided by a grant from the John and Mary R. Markle Foundation; funds for technical assistance were supplied by the Graduate College, State University of Iowa.

through the courtesy of Dr. R. W. Vilter, were found to have only about one-half the normal amount of prothrombin.

In recent studies at the University Hospital we have extended these preliminary observations on pernicious anemia. In addition, we now have data to show that this hypoprothrombinemia is not appreciably affected by the administration of vitamin K. Following the institution of liver therapy, however, there is an abrupt rise in the prothrombin level.

Material and Method. Twenty cases of Addisonian pernicious anemia, admitted to the University Hospital, were made available for study by the staffs of the Departments of Medicine, Neurology and Urology. The diagnosis was based on the history, and the clinical and laboratory findings, together with the hematologic response to liver extract.

Twelve of the 20 cases received daily intramuscular injections of 1 to 5 cc. of liver extract (Lilly or Lederle, 15 U.S.P. units per cubic centimeter). Of these 12, 7 were given vitamin K for 3 to 6 days prior to the institution of liver therapy. As a source of vitamin K activity we administered 2-methyl-1, 4-naphthoquinone in 5 of the cases (6 mg. daily, given in corn oil, along with bile salts). Instead of this compound, 2 cases received daily intravenous injections of 1 mg. of 4-amino-2-methyl-1-naphthol ("Synkamin" *). Prothrombin determinations were made by the two-stage method of Warner, Brinkhous and Smith.^{4,5a}

TABLE 1.—PROTHROMBIN VALUES IN PATIENTS WITH PERNICIOUS ANEMIA.

Case No.	Erythrocyte hematocrit, %.	Prothrombin, % of normal.	Central nervous system damage.†
1	11	40	++
2	14	46	++++
3	15	52	++
4	17	50	+
5	18	45	0
6	19	45	+++
7	19	52	+++
8	20	40	+++
9	20	56	++++
10	20	68	++
11	21	42	+
12	22	59	+++
13	23	47	+++
14	24	42	++
15	26	73	++
16	27	47	+++
17	29	43	++
18	29	60	++
19	31	82	++
20	35	58	++++

† Central nervous system damage estimated as follows: 0, no subjective or objective findings; +, paresthesia; ++, mild objective findings; +++, marked objective findings; +++++, cord degeneration to the point of paralysis.

Results. The prothrombin values obtained at the time of admission in this group of cases are shown in Table 1. The cases are listed in order of hematocrit values. Only 3 of the patients showed prothrombin values greater than two-thirds of the normal level, and in 10 (one-half of the cases) the values were less than one-half

* The "Synkamin" used in this study was kindly furnished by Parke, Davis & Co.

of the normal. There is some tendency for the lowest values to occur in the cases in which the anemia is severe. However, it is evident from the table that the degree of anemia and the degree of hypoprothrombinemia are not closely correlated. There is no correlation whatever between the degree of prothrombin deficiency and the amount of nervous system damage.

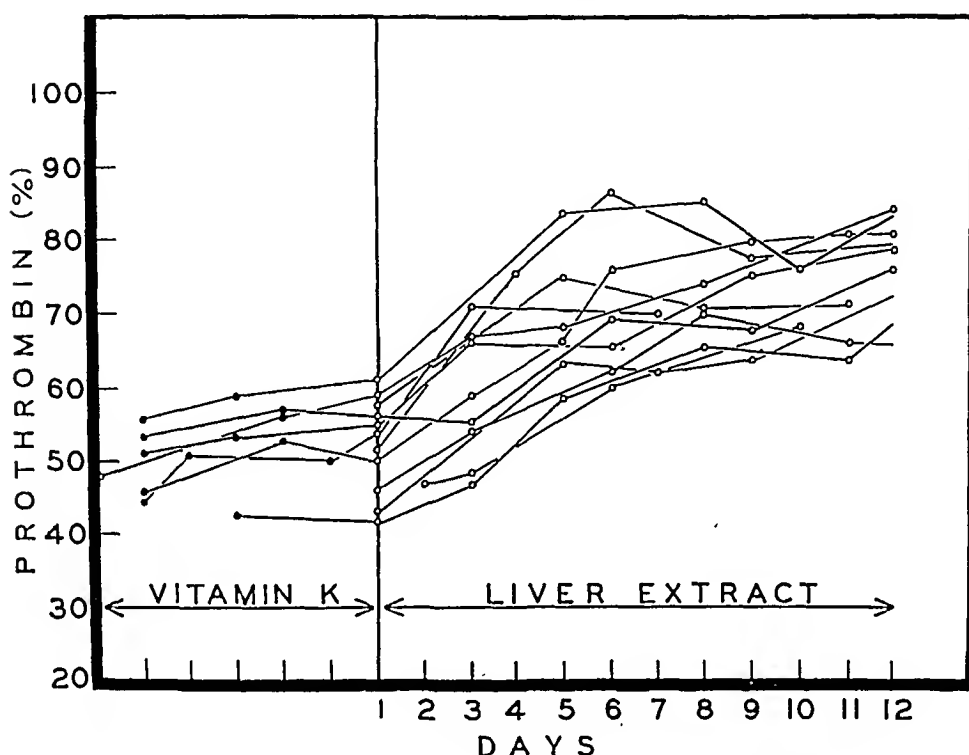


CHART 1.—Prothrombin response to therapy in pernicious anemia (12 cases).

The effect of therapy on the prothrombin level of the treated cases is shown in Chart 1. The first part of the chart shows that the administration of large amounts of vitamin K had no consistent influence on the prothrombin values. The very slight improvement seen in a few of the cases is not more than might result from general improvement incident to bed rest. The last part of the chart shows, in contrast, that the level rises rapidly following the institution of liver therapy. The rise was somewhat more rapid than the corresponding increase in circulating red cells, and was much greater than could result from simple concentration of the plasma due to increase in the hematocrit. Maximum prothrombin values, reached in about 1 week, were maintained. The prothrombin level did not, however, rise to quite normal values, and in general, the level ultimately reached was higher in the cases having the higher initial values. In the majority of the cases the daily dose of liver extract was 1 cc.; a few given larger amounts showed no greater prothrombin response.

Discussion. The lowest prothrombin value observed in these cases, 40% of normal, is above the level at which bleeding ordinarily occurs, and none of the cases showed any clinical evidence of hemorrhage. It is perhaps significant, however, that the clotting power of the blood, as measured by the one-stage prothrombin methods, is essentially normal. Thus, the prothrombin levels in these cases, by both the "bedside" test^{8b} and by the method of Quick,² were found to be within normal limits, and were not modified by treatment. The biologic significance of the failure of the one-stage tests to agree with the two-stage method, in certain conditions, is not yet apparent. The suggestion of Quick and Grossman³ that the two-stage method may be affected by variation in other plasma proteins receives no support in the present instance. Plasma protein determinations in a number of our cases yielded values for both the total protein and the albumin-globulin ratios which were within normal limits, and which were not altered by treatment. Perhaps some compensatory mechanism, as has been suggested in other conditions,^{1, 5b, 8a} permits a more ready utilization of the prothrombin available in pernicious anemia.

The basic reason for the prothrombin fall reflected by the two-stage method is at present obscure. It is not obviously related to the anemia itself, for many long-standing cases of secondary anemia and of aplastic anemia show no depression whatever. Even in pernicious anemia the change is not clearly related to the degree of anemia.

The beneficial effects of liver therapy might seem to imply that the liver extract supplies some unknown factor needed for prothrombin production. However, it is, perhaps, even more likely that the rise in the prothrombin level is related to improvement in function of some organ—the liver for example. It is known that the liver is concerned in the manufacture of prothrombin, and studies on the excretion of urobilinogen⁷ do, in fact, suggest mild hepatic insufficiency in cases of pernicious anemia. The prothrombin response in pernicious anemia may be related to the response in red cell production, but any such relationship is not yet apparent. In any case, the beneficial effect of liver extract on the production of prothrombin appears to be confined to cases of pernicious anemia. We have administered liver extract to newborn infants, as well as to patients with Laennec's cirrhosis and to patients with obstructive jaundice. The hypoprothrombinemia present in such cases did not respond to the liver extract. Likewise, the mild hypoprothrombinemia seen in debilitated patients does not respond to this form of treatment.

Summary. Patients with Addisonian pernicious anemia in relapse usually show considerable decrease in plasma prothrombin. In the majority of such cases, the prothrombin level is found to be between 40% and 65% of the normal. The hypoprothrombinemia is not rectified by large doses of vitamin K. When specific liver

therapy is instituted, the plasma prothrombin level promptly shows a marked rise.

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INFLUENCE OF ACTIVE AND INACTIVE ANTIANEMIC PRINCIPLES UPON THE ERYTHROCYTES OF THE IMMATURE OPOSSUM (*DIDELPHYS VIRGINIANA*).

By JOSEPH STASNEY, M.D., M.S.,

INSTRUCTOR IN PATHOLOGY AND BACTERIOLOGY, THE SCHOOL OF MEDICINE OF LOUISIANA STATE UNIVERSITY,

AND

EDWARD L. BURNS, M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, THE SCHOOL OF MEDICINE OF LOUISIANA STATE UNIVERSITY,
NEW ORLEANS, LA.

(From the Departments of Pathology and Bacteriology of the School of Medicine of Louisiana State University and Charity Hospital of Louisiana.)

BECAUSE of certain similarities between the erythrocytes of mammalian fetuses and those of patients with pernicious anemia⁹ attempts have recently been made to influence the rate of maturation of fetal erythrocytes by the experimental administration of antianemic principles to animals during gestation.⁸ Adequately controlled studies have shown demonstrable changes in the peripheral blood and bone marrow of treated mothers, although this observation has not been confirmed by all observers. Sehlicke,⁶ in the largest series of experimental animals reported to date, has confirmed the original observation that normal gastric juice, when administered to pregnant albino rats, influences the rate of maturation of the fetal red blood cells. He also reviewed comprehensively the controversial observations of the various workers in this field, his review including all but the two most recent reports,^{3,5} in both of which the writers failed to secure results by this method.

The inaccessibility of common mammalian fetuses to direct injection made it desirable to find a species in which antianemic principles could be injected directly into the developing animals rather than into the mothers. The marsupial opossum (*Didelphys virginiana*) is a suitable animal for this purpose, as we have pointed out in a preliminary study,⁷ because in this species, after an intra-

uterine life of approximately 12 days,^{2,4} the immature young live in the maternal pouch for 90 days. In this same study⁷ we also reported observations which indicated that pouch opossums had a macrocytic anemia, as compared to adult animals, and that the direct injection of antianemic principles into the immature animals in the maternal pouch reduced the size of their erythrocytes.

Materials and Methods. The studies reported in this paper were carried out on 6 adult male opossums, 4 adult non-pregnant female opossums and 117 immature opossums. The immature opossums were contained in the pouches of 18 adult female opossums. The adult animals were trapped in Louisiana and Mississippi during the winter months of 1939 and 1940.

During the experimental period each adult animal was housed in a separate cage and fed a diet consisting of fresh Purina dog chow, bone meal, milk and water.

The number of young animals found in a single pouch varied from 5 to 9. Forty-nine were used in 1939. The crown-rump lengths of the animals in this year varied from 5.5. to 7 cm. and averaged 6.39 cm. at the beginning of the experiment. No significant variations were noted in the size of the litter mates. Sixty-eight animals were used in 1940. The crown-rump lengths in this year varied from 5.5 to 7 and averaged 6.62 cm. at the beginning of the experiment. Slight variations were noted in the size of the litter mates.

The animals in each pouch were divided into 2 groups, one of which consisted of treated animals and the other of untreated controls. Each animal was identified by an ear puncture.

The immature opossums in the various maternal pouches were divided into 5 groups, as follows:

Group I. Thirty-nine animals. Twenty experimental and 10 control animals were used in 1939, and the studies were repeated on 5 experimental and 4 control animals in 1940. The treated animals were given daily intraperitoneal injections of concentrated normal human gastric juice, in doses varying from 0.1 to 0.2 cc., for periods varying from 3 to 13 days. The total amount administered varied from 0.8 to 2.2 cc. The gastric juice, which was secured from normal subjects after injection of histamine, was prepared from several samples, which were pooled, filtered, concentrated 10 times by evaporation, and neutralized with NaOH just before being used. This material presumably contained the intrinsic factor of Castle; no attempt was made to determine the presence or absence of the extrinsic factor.

Group II. Twenty-six animals. Nine experimental and 10 control animals were used in 1939, and the studies repeated on 4 experimental and 3 control animals in 1940. The treated animals were given daily intraperitoneal or subcutaneous injections of a concentrated solution of liver extract (Lederle, 1 cc. containing 15 U.S.P. units),* in doses varying from 0.1 to 0.2 cc., for periods varying from 3 to 14 days. The total amount administered varied from 0.3 to 2.6 cc.

* Generously supplied by the Lederle Laboratories, Inc., New York.

Group III. Twenty-six animals, 16 of which were treated and 10 of which served as untreated litter mate controls. All the experiments were carried out during 1940. The treated animals were given daily intraperitoneal injections of inactivated concentrated normal human gastric juice, in doses varying from 0.1 to 0.2 cc., for periods varying from 5 to 11 days. The total amount administered varied from 1 to 2.2 cc. The gastric juice was prepared by the method already described; inactivation was accomplished by heating it to 100° C. for 15 minutes.

Group IV. Eighteen animals, 11 of which were treated and 7 of which served as untreated litter mate controls. All the experiments were carried out during 1940. The treated animals were given daily subcutaneous injections of an inactivated concentrated solution of liver extract (Lederle, 1 cc. containing 15 U.S.P. units), in doses varying from 0.1 to 0.2 cc., for periods varying from 2 to 10 days. The total amount administered varied from 0.4 to 1.5 cc. The liver extract was inactivated by heating it in the autoclave to 121.5° C. under 15 pounds of pressure for 30 minutes.

Group V. Eight animals, 5 of which were treated and 3 of which served as untreated litter mate controls. All the experiments were carried out during 1940. The treated animals were given 6 daily intraperitoneal injections of 0.2 cc. of concentrated gastric juice obtained from a patient with Addisonian pernicious anemia. The gastric juice was prepared by the method already described; neutralization with NaOH was unnecessary.

Blood was obtained from every immature animal in both treated and control groups at the beginning and the end of each experiment by cutting the tail vein, heparin being used as an anticoagulant. Only a few drops of blood were collected from each animal. The blood samples from the 6 adult male and 4 adult non-pregnant female opossums were secured by cardiac puncture.

The following determinations, the data from which were all analyzed statistically,¹ were carried out on each sample of blood:

1. Total number of red blood cells per c.mm., by the use of standardized pipettes.

2. Percentage of packed red blood cells in the whole blood, by the use of the Van Allen type of hematocrit and centrifugalization at 2400 revolutions per minute for 15 minutes.

3. Mean corpuscular volume, computed according to the method of Wintrobe.

4. Mean maximal diameter of the red blood cells. This value was obtained by measuring, at a magnification of 1000 times, from 100 to 200 red blood cells, which were stained with Wright's stain and focussed on a ground glass plate. Measurement of the mean maximal diameter of the red blood cells was obtained in all cases, but technical difficulties made some of the other determinations impossible, as indicated by Tables 1 to 5.

TABLE 1.—EFFECT OF NORMAL HUMAN GASTRIC JUICE ON ERYTHROCYTES OF POUCH OPOSSUMS (GROUP I).

Values.	Before treatment.		After treatment.	
	Experimental.	Control.	Experimental.	Control.
Number of animals	24	12	24	12
<i>RBC* in mill./c.mm.</i>	2.186	2.187	2.534	2.190
Variance of means	0.0012	0.0024	0.0045	0.0029
Difference	0.001		0.344	
t	0.0017		4.0070	
P	0.9		>0.01	
Number of animals	24	12	24	12
<i>Volume of packed RBC*, %</i> . .	34.67	35.20	29.06	33.95
Variance of means	0.2317	0.3542	0.6629	0.8608
Difference	0.53		4.89	
t	0.6925		3.9618	
P	0.5		>0.01	
Number of animals	24	12	24	12
<i>Mean corpuscular volume of RBC* in cubic microns</i> . .	158.75	161.75	114.75	156.33
Variance of means	9.0833	13.3121	5.8964	21.1455
Difference	3.0		41.58	
t	0.6339		7.9959	
P	0.5		>0.01	
Number of animals	25	14	25	14
<i>Mean maximal diameter of RBC* in microns</i> . .	8.988	9.157	7.920	8.828
Variance of means	0.0039	0.0093	0.0023	0.0040
Difference	0.169		0.908	
t	1.4698		11.4574	
P	0.2		>0.01	

* Average values. *RBC* = erythrocytes.

TABLE 2.—EFFECT OF CONCENTRATED LIVER EXTRACT ON ERYTHROCYTES OF POUCH OPOSSUMS (GROUP II).

Values.	Before treatment.		After treatment.	
	Experimental.	Control.	Experimental.	Control.
Number of animals	7	10	7	10
<i>RBC* in mill./c.mm.</i>	2.017	2.118	2.807	2.331
Variance of means	0.0060	0.0038	0.0019	0.0051
Difference	0.101		0.476	
t	1.0197		5.7056	
P	0.3		>0.01	
Number of animals	7	10	7	10
<i>Volume of packed RBC*, %</i> . .	32.29	34.10	33.09	35.47
Variance of means	0.8436	0.4918	2.3798	0.7809
Difference	1.81		2.38	
t	1.5662		1.3387	
P	0.1		0.2	
Number of animals	7	10	7	10
<i>Mean corpuscular volume of RBC* in cubic microns</i> . .	158.00	160.90	117.28	152.80
Variance of means	6.0952	12.6766	15.0028	37.7733
Difference	2.90		35.52	
t	0.6693		4.8893	
P	0.5		>0.01	
Number of animals	13	13	13	13
<i>Mean maximal diameter of RBC* in microns</i> . .	9.030	8.938	8.000	9.000
Variance of means	0.0081	0.0042	0.0189	0.0040
Difference	0.092		1.000	
t	0.9042		6.6111	
P	0.4		>0.01	

* Average values. *RBC* = erythrocytes.

TABLE 3.—EFFECT OF INACTIVATED NORMAL HUMAN GASTRIC JUICE ON ERYTHROCYTES OF POUCH OPOSSUMS (GROUP III).

Values.	Before treatment.		After treatment.	
	Experimental.	Control.	Experimental.	Control.
Number of animals	16	10	16	10
RBC* in mill./c.mm.	2.378	2.354	2.591	2.643
Variance of means	0.0045	0.0035	0.0043	0.0099
Difference	0.024		0.052	
t	0.2677		0.4336	
P	0.8		0.7	
Number of animals	16	10	16	10
Volume of packed RBC,* %	33.28	33.10	31.31	31.50
Variance of means	0.2542	0.2989	0.8414	0.8611
Difference	0.18		0.19	
t	0.2420		0.1456	
P	0.8		0.9	
Number of animals	16	10	16	10
Mean corpuscular volume of RBC* in cubic microns	140.62	141.00	121.37	120.60
Variance of means	5.6875	3.6888	11.8416	30.8933
Difference	0.38		0.77	
t	0.0124		0.0117	
P	0.9		0.9	
Number of animals	16	10	16	10
Mean maximal diameter of RBC* in microns	8.27	8.29	8.08	8.09
Variance of means	0.0071	0.0096	0.0033	0.0017
Difference	0.02		0.01	
t	0.1546		0.1422	
P	0.9		0.9	

* Average values. RBC = erythrocytes.

TABLE 4.—EFFECT OF INACTIVATED CONCENTRATED LIVER EXTRACT ON ERYTHROCYTES OF POUCH OPOSSUMS (GROUP IV).

Values.	Before treatment.		After treatment.	
	Experimental.	Control.	Experimental.	Control.
Number of animals	10	7	10	7
RBC* in mill./c.mm.	2.347	2.394	2.355	2.701
Variance of means	0.0106	0.0107	0.0158	0.0059
Difference	0.047		0.346	
t	0.3221		2.3505	
P	0.7		0.05	
Number of animals	10	7	10	7
Volume of packed RBC,* %	32.35	32.35	29.65	32.21
Variance of means	0.2781	0.2231	0.6059	0.0940
Difference	0		2.56	
t	0		3.0600	
P	0		>0.01	
Number of animals	10	7	10	7
Mean corpuscular volume of RBC* in cubic microns	139.10	136.14	127.70	119.85
Variance of means	57.0777	29.5714	18.5666	11.0714
Difference	2.96		7.85	
t	0.3223		1.4511	
P	0.3		0.2	
Number of animals	11	7	11	7
Mean maximal diameter of RBC* in microns	8.272	8.271	8.090	8.071
Variance of means	0.0050	0.0033	0.0021	0.0014
Difference	0.001		0.019	
t	0.0109		0.3376	
P	0.9		0.7	

* Average values. RBC = erythrocytes.

TABLE 5.—EFFECT OF CONCENTRATED HUMAN GASTRIC JUICE FROM A SUBJECT WITH ADDISONIAN PERNICIOUS ANEMIA ON ERYTHROCYTES OF POUCH OPOSSUMS (GROUP V).

Values.	Before treatment.		After treatment.	
	Experi- mental.	Control.	Experi- mental.	Control.
Number of animals	5	3	5	3
RBC* in mill./c.mm.	2.47	2.45	2.12	2.31
Volume of packed RBC,* %	35.10	33.67	28.80	28.33
Mean corpuscular volume of RBC* in cubic microns	143.6	137.6	136.2	122.3
Mean maximal diameter of RBC* in microns	8.70	8.73	8.62	8.46

* Average values. RBC = erythrocytes.

Results. At the beginning of the experiments the average total number of erythrocytes in the 117 immature pouch opossums was 2,265,000 per c.mm., as compared with 4,420,000 per c.mm. in the 10 adult animals. The average mean maximal diameter of the erythrocytes was 8.72 microns in the immature animals, as compared with 7.30 microns in the adult animals. The average mean corpuscular volume was 150 cubic microns in the immature animals, as compared with 87.99 cubic microns in the adult animals. Before treatment the bloods of the experimental animals and of their litter mate controls showed no significant differences in any of the values determined (Tables 1 to 5).

TABLE 6.—DISTRIBUTION OF ERYTHROCYTES ACCORDING TO DIAMETERS BEFORE AND AFTER TREATMENT.

	Number of animals.	Before treatment, cell diameters, %.			After treatment, cell diameters, %.		
		<8.5	8.5-9.5	>9.5	<8.5	8.5-9.5	>9.5
<i>Concentrated Normal Human Gastric Juice.</i>							
Experimental	20	22.00	63.45	14.50	72.10	24.92	2.97
Control	10	19.30	59.65	21.05	25.00	62.60	12.40
<i>Concentrated Liver Extract.</i>							
Experimental	9	23.61	61.70	14.68	62.61	32.37	5.00
Control	10	23.70	63.70	12.60	21.45	62.00	16.55
<i>Inactivated Concentrated Normal Human Gastric Juice.</i>							
Experimental	16	50.25	45.20	4.55	55.71	41.00	3.29
Control	11	44.33	49.66	6.00	60.66	37.08	2.25
<i>Inactivated Concentrated Liver Extract.</i>							
Experimental	11	49.33	47.66	3.00	60.06	37.80	2.13
Control	7	47.71	49.28	3.00	59.40	38.50	2.00
<i>Concentrated Human Gastric Juice From Subject With Pernicious Anemia.</i>							
Experimental	5	25.83	65.50	8.66	33.62	54.37	12.00
Control	3	25.33	67.66	7.00	39.40	47.80	12.80

The results of treatment in the various groups can be summarized as follows:

Group I. Effect of normal concentrated human gastric juice (Table 1): After treatment, in the experimental as compared to the control group, the mean number of red blood cells was significantly

increased and their mean packed volume, average mean corpuscular volume and average mean maximal diameter were significantly decreased. The decrease in the last three values was due to a relative increase in the number of smaller erythrocytes (Table 6), the change being graphically shown by a shift to the left of the Price-

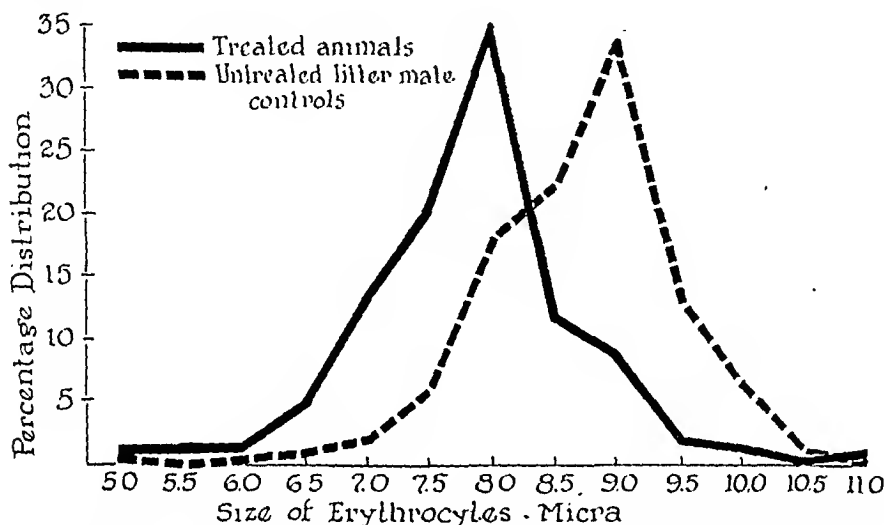


CHART 1.—Effect of normal concentrated human gastric juice on the percentage distribution, according to size, of the erythrocytes of pouch opossums.

Jones curve (Chart 1). The smaller erythrocytes showed a distribution of hemoglobin similar to that seen in mature red blood cells, thus differing from the uniformly hyperchromatic macrocytes of the fetal blood (Fig. 1).

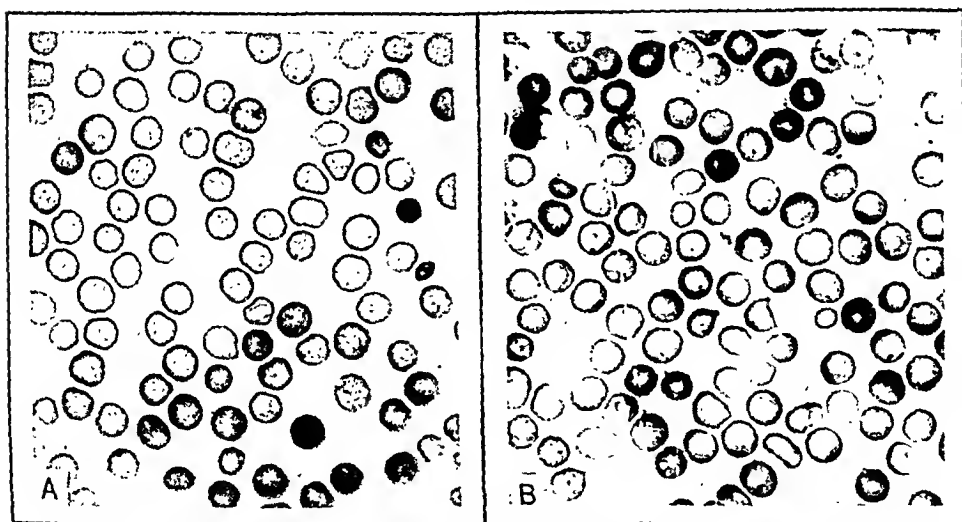


FIG. 1.—A, Erythrocytes of an untreated pouch opossum of 7.5 cm. crown-rump length. Hemoglobin tends to be evenly distributed throughout the cell. (Wright's stain, $\times 495$.) B, Erythrocytes of a litter mate pouch opossum treated with normal concentrated human gastric juice for 4 days (0.8 cc.). The hemoglobin tends to be distributed toward the periphery of the cell. (Wright's stain, $\times 495$.)

Group II. Effect of concentrated solution of liver extract (Table 2): After treatment, in the experimental as compared to the control groups, the mean number of red blood cells was significantly increased and their average mean corpuscular volume and average mean maximal diameter were significantly decreased. There was no significant change in the mean volume of the packed red blood cells. The decrease in the average mean values for the corpuscular volume and maximal diameter of the cells was due (Table 6) to a relative increase in the number of smaller erythrocytes, the change being graphically shown by a shift to the left of the Price-Jones curve (Chart 2). The smaller erythrocytes, as in Group I, showed a distribution of hemoglobin similar to that seen in mature red blood cells.

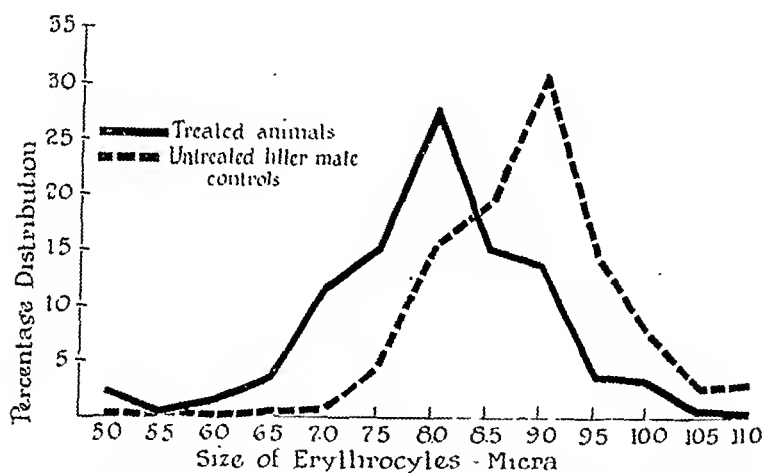


CHART 2.—Effect of concentrated liver extract solution (Lederle) on the percentage distribution, according to size, of the erythrocytes of pouch opossums.

Group III. Effect of inactivated concentrated normal human gastric juice (Table 3): After treatment, in the experimental as compared to the control group, there was no significant change in any of the values determined. The cell distribution according to diameters (Table 6) was essentially the same at the end of the experiment in both groups, and the hemoglobin was uniformly distributed throughout the cytoplasm of the erythrocytes of both control and treated animals.

Group IV. Effect of inactivated concentrated solution of liver extract (Table 4): After treatment, in the experimental as compared to the control group, there was a suggestive but not significant reduction in the mean number of red blood cells and a significant reduction in the mean volume of these packed cells. The other values were not significantly changed. The cell distribution according to diameters, as in Group III, was essentially the same

at the end of the experiment in both treated and control groups (Table 6), and the hemoglobin was uniformly distributed throughout the cytoplasm in all the animals.

Group V. Effect of administration of concentrated human gastric juice from a patient with Addisonian pernicious anemia (Table 5): After treatment there were no significant differences between the erythrocytes of the control and experimental groups, and the cell distribution according to diameters was essentially the same in both groups. Because of the small number of animals used the results of the statistical analyses of these data are not included in Table 5.

In the experiments reported in Groups III, IV, and V, all of which were performed in 1940, the immature opossums found in the pouches were somewhat larger than those found in 1939. As a result, the number of red blood cells per c.mm. was somewhat greater and the average mean corpuscular volume and average mean maximal diameter were somewhat less at the beginning of the experiments than these respective values for the animals studied in 1939 (Tables 1 to 5).

Inactivated gastric juice was slightly toxic for the experimental animals, as indicated by their general appearance compared to that of their untreated litter mate controls, and by the death of several of the animals. The same observation was made concerning the inactivated concentrated liver extract used in Group IV and the gastric juice from the patient with Addisonian pernicious anemia used in Group V, although in the latter experiment none of the animals died.

Comment. Our comparative studies of untreated adult opossums and untreated immature pouch opossums showed differences between the erythrocytes of the two groups. The young animals, as compared with the adult animals, showed an anemia and also showed a relative macrocytosis, as indicated by the larger mean corpuscular volume and the greater mean maximal diameter of the red blood cells. Morphologically, the hemoglobin of the majority of the erythrocytes of the immature animals was distributed evenly throughout the cells, whereas in the adults it was usually more concentrated at the periphery of the cells and the central zones were relatively clear. As the young animals matured, the anemia improved and the number of macrocytes decreased until eventually the red blood cells resembled those of the adult animals in both numbers and appearance.

Studies of the action of normal human gastric juice and of concentrated liver extract solution showed that after the administration of these substances the average number of red blood cells was relatively increased and their average size was relatively decreased. As has been pointed out, the diminution in the average size of the erythrocytes was caused by an increase in the number of smaller

cells, which morphologically resembled the erythrocytes found in the adult animals. As these smaller cells increased in numbers, the blood pictures of the treated animals approached those of the adult animals, although in no instance did they become identical with them.

Normal human gastric juice and concentrated liver extract solution altered to approximately the same degree all the values determined except the mean packed volume of red blood cells. This value was significantly reduced by the administration of gastric juice, but was not significantly altered by the liver extract solution. Such findings suggest that the gastric juice reduced the size of the erythrocytes proportionately more than it increased the number, whereas the concentrated liver extract affected both values proportionately (Tables 1 and 2).

According to these experiments, when the thermolabile factor in human gastric juice was destroyed by heating, the maturation of the red blood cells in the mammalian fetus was not accelerated (Table 3). A similar observation was made when the antianemic principles in concentrated liver extract were destroyed by heating (Table 4). Injections of the inactivated extract, furthermore, not only failed to accelerate normal maturation of the cells, but may actually have influenced it adversely. During the course of the experiment (Table 4) the mean number of erythrocytes in the control group somewhat increased, but the mean number in the experimental group remained at essentially the same level, which suggests that the inactivated liver extract solution may have inhibited the normal increase in number. On the other hand, although the inactivated liver extract solution apparently suppressed the number of red blood cells, it had no effect upon the average mean maximal diameter of these cells in the experimental as compared to the control groups (Table 4). At the end of the experiment there was therefore a significant reduction in the packed volume of the red blood cells in the treated as compared to the untreated animals. This apparent inhibition of normal maturation suggests that toxic elements were formed in the liver extract solution as a result of heating.

It is important to note again that the animals used for testing inactivated human gastric juice and inactivated concentrated liver extract solution showed greater variations in size than those used for testing the active principles, and were somewhat larger. As a result, the number of erythrocytes was somewhat greater and the size of these cells somewhat smaller at the beginning of the experiments with inactivated principles than at the beginning of the experiments with active antianemic principles. It is possible that the variations in size of the animals may account for some of the irregularities in the numerical data in the experiments with inactivated materials. We are inclined to believe that the size (age) of

the animals has considerable bearing on the results, and that opossums with uniform crown-rump lengths of 5 to 6 cm., with erythrocytes measuring as near 9 microns in diameter as possible, are optimum for such studies. It would be advantageous if future studies were carried out on the basis of these criteria.

The number of animals which received gastric juice from a patient with Addisonian pernicious anemia was too small to permit definite conclusions as to the action of this substance, and the experiments should be repeated with a larger series. The data suggest, however, that gastric juice secured from this source not only failed to accelerate the development of the erythrocytes but also may have slightly retarded their maturation.

These studies show that the red blood cells of the immature opossum are constantly larger than those of adults of the same species. As the pouch animals normally mature, the erythrocytes become smaller and eventually approximate in numbers, size and appearance those found in adult animals. Similarly, the erythrocytes of patients with pernicious anemia are relatively larger during relapses of the disease, whereas remissions are always associated with a reduction in the size and a change in the appearance of these cells. These similarities suggest that in the developing opossums the principles required for the complete maturation of the red blood cells may be lacking, just as they have been shown to be lacking in patients with pernicious anemia. As the animals mature in the maternal pouch, the necessary principles presumably become available and the signs of deficiency, as reflected in the blood picture, therefore gradually disappear. This hypothesis is substantiated by the observation that the experimental administration of anti-anemic principles to immature opossums significantly alters the character of their red blood cells.

Summary. 1. Studies on immature developing opossums, living in the maternal pouch, showed a macrocytic anemia in these animals as compared with adult animals of the same species. As the young animals matured, the character of their red blood cells gradually changed until it assumed that of adult animals.

2. The direct injection of either concentrated normal human gastric juice or of a concentrated solution of liver extract significantly reduced the mean maximal diameter and the mean corpuscular volume of the erythrocytes, and significantly increased their number, in the treated pouch opossums as compared with their untreated litter mate controls. These changes were effected through a relative increase in the number of smaller erythrocytes.

3. The direct injection of inactivated normal human gastric juice, of inactivated concentrated liver extract solution, and of gastric juice from a patient with Addisonian pernicious anemia failed to increase significantly the number of red blood cells or to reduce significantly the mean maximal diameter and the mean

corpuscular volume of these cells in the treated pouch opossums as compared to their untreated litter mate controls.

ADDENDUM. After this paper was submitted for publication, there appeared a review by O. P. Jones: *Transmission of the Antianemic Principles Across the Placenta and Its Influence on Embryonic Erythropoiesis* (Arch. Int. Med., 68, 476, 1941), in which he cites our preliminary report (Proc. Soc. Exp. Biol. and Med., 42, 544, 1939) and remarks in a footnote that the diameters of only the largest red blood cells were measured in our studies. This interpretation of our method of measuring cell diameters is incorrect and may have arisen from our use of the term "mean maximal diameter." In our work there was no selection of cells. On each blood smear, every cell was measured in turn until 100 or 200 cells had been encountered. Because the cell outlines did not always form perfect circles, however, the greatest—or maximal—diameter of each cell was selected for measurement.

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SYPHILITIC AORTIC INSUFFICIENCY: THE ASYMPTOMATIC PHASE.*

BY WALSH McDERMOTT, M.D.,

INSTRUCTOR IN MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,

RALPH R. TOMPSETT, M.D.,

ASSISTANT RESIDENT IN MEDICINE, NEW YORK HOSPITAL,

AND

BRUCE WEBSTER, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK, N. Y.

(From the Syphilis Clinic of the New York Hospital and the Department of Medicine, Cornell University Medical College.)

DURATION of life, after the onset of symptoms due to syphilis of the aortic valve, is generally stated to be relatively short.^{1,3,11,15,21} The picture described in the standard texts is one of the rapid developments of symptoms and signs of cardiac insufficiency in a patient in the forties or fifties who had previously been perfectly active and well.^{1,3,11,15,21} It is generally agreed among the various authorities that survival from this stage on is usually a matter of only 1 or 2 years.¹² It is recognized¹² that the use of specific antisiphilic therapy in aortic syphilis will prolong life, even doubling the average expectancy, but the emphasis in practically all authoritative works

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is on the clinical course after the onset of failure with but passing reference to the course before failure appears.

Yet in the study of 1000 cardiacs, 10 years after the original examination, Grant⁵ has shown that the 10-year mortality associated with syphilis of the aortic valve is only 64%, actually less than the mortality rate over the same period of patients with mitral stenosis with auricular fibrillation (68%).

This discrepancy between the poor prognosis usually accorded patients with syphilitic aortic regurgitation after the onset of symptoms, and the 10-year statistics of Grant, is a reflection of the differences between two types of clinical material. Grant's patients were all ambulatory men who were either in, or being considered for military service. Relatively few of these men would have had examinations of their hearts at that time under normal conditions. The aortic syphilis seen by most internists is not selected from large groups of ambulatory patients with syphilis, but is seen in individuals who have sought medical care because of symptoms of cardiac insufficiency. This suggests that aortic insufficiency due to syphilis is actually present in a clinically recognizable form for a relatively lengthy period of time before the development of symptoms, but that because of this asymptomatic state the patients do not seek medical care and hence are not discovered. Obviously the only way patients with this asymptomatic form of valvular syphilis can be discovered is by doing routine physical examinations on all known syphilitics.

During the 4½-year period from October, 1936, to April, 1941, 2718 syphilitic patients were examined in the syphilis clinic of this hospital, and 100 (3.6%) were found to have syphilitic aortic insufficiency. Nine of these had aneurysms as well, leaving 91 (3.3%) patients with the valvular defect alone. The diagnosis in every case was confirmed by two or more observers. Our criterion was the repeatedly demonstrable presence of a diastolic murmur over the aortic area or down the left sternal border in a patient known to have been infected with syphilis and who had no evidence of mitral stenosis or congenital heart disease either clinically or by Roentgen ray.

The patients were all examined on numerous occasions. It is frequently observed that a murmur, difficult to detect or inaudible with the patient in the recumbent position, can be brought out by having the patient sit up, lean forward and expire forcibly. The precordium is then examined while the patient holds his breath in full expiration.

During this period we were soon impressed by the fact that the presenting clinical picture and subsequent course of the disease in the majority of these patients differed sharply from that of the classical descriptions, particularly in respect to their ability to do work without symptoms or signs of cardiac insufficiency. Accord-

ingly, a clinical study of all of our patients with syphilitic aortic insufficiency without aneurysm has been made to obtain information on this asymptomatic phase of the disease.

Of the 91 patients with aortic valvular syphilis, 45 (49%), or nearly one-half of the group, had no symptoms of cardiac insufficiency at the time of the original diagnosis. An additional 13 (14%) admitted symptoms only after specific questioning but had not sought medical care because of these symptoms; and 33 (36%) patients had definite symptoms related to their aortic disease. On this basis of the clinical impression of the status of the individual patient at the time of diagnosis three groups were formed: Group I (asymptomatic), Group II (symptoms on questioning only); and Group III (symptomatic).

By asymptomatic is meant that all of these patients denied any exertional dyspnea, orthopnea, substernal pain on effort or at rest, palpitation or ankle edema. The majority were working and all of them were completely unaware of the fact that they had heart disease. The patients in the symptomatic group (Group III) presented the picture more generally regarded as typical of syphilitic aortic regurgitation. The presenting complaint in each case was directly referable to the cardiovascular system, and in many, angina of effort and symptoms suggesting failure were present.

TABLE 1.—PATIENTS FOLLOWED MORE THAN 2 YEARS.

Group.	No. of patients	Dead.		Living but have developed symptoms.
		Died of heart disease.	Died of other cause.	
I (Asymptomatic)	20	1	1	1
II (Symptoms on questioning only)	8	1	0	0
III (Symptomatic)	15	1	1	
Total	43	3	2	

Period of Observation. Twenty patients, or almost one-half of the asymptomatic group (Group I), have been followed for more than 2 years (Table 1). Two of these 20 have died, both $2\frac{1}{2}$ years after the diagnosis, one of his heart disease and the other of a carcinoma of the bladder. Two patients of the 25 who have been followed for less than 2 years have died, one of a gastric carcinoma and the other of paresis (Table 2). Two patients of this entire Group I have developed symptoms under observation. One developed slight exertional dyspnea 3 months after the diagnosis was made and angina of effort 4 months later. The other patient who has been followed for more than 7 years has developed slight dyspnea on climbing to his fourth floor room within the past year. However, he has such marked loss of vision that he is forced to proceed much more slowly than normal so that it is highly probable that he would have more marked symptoms if he were able to be more active.

Eight of the 13 patients in Group II (symptoms on questioning only) have been followed for more than 2 years. One of this group died $3\frac{1}{2}$ years after the diagnosis, presumably because of heart disease.

Fifteen of the 33 patients in Group III (symptomatic) have been followed for more than 2 years. Eight of the entire group have died, 2 of carcinoma and the others as a result of their heart disease.

Thus, of the entire group of 91 patients with aortic valvular syphilis, 43 (46%), or almost one-half, have been followed for more than 2 years. The follow-up by years is recorded in Table 3.

TABLE 2.—PATIENTS FOLLOWED LESS THAN 2 YEARS.

Group.	No. of patients.	Dead.		Living but have developed symptoms.
		Died of heart disease.	Died of other cause.	
I (Asymptomatic)	25	0	2	1
II (Symptoms on questioning only)	5	0	0	1
III (Symptomatic)	18	5	1	
Total	48	5	3	

TABLE 3.—PERIOD OF OBSERVATION OF 91 PATIENTS WITH SYPHILITIC AORTIC INSUFFICIENCY.

Years of observation.*	Number of patients.		
	Group I.	Group II.	Group III.
Less than 1	14	2	11 (5 deaths)
1- 2	11	3	7 (1 death)
2- 3	8	2	8 (1 death)
3- 4	5	5	1
4- 5	2	1	3 (1 death)
5- 6	0	..	1
6- 7	1	..	2
7- 8	2		
8- 9	0		
9-10	2		
	45	13	33 (8 deaths)
	(4 deaths)	(1 death)	

* Records were available of some of these patients who had been under observation in this institution before this clinic was started.

Any symptomatic classification of cardiac patients based solely on the history and physical examination has certain obvious sources of error. The most prominent of these is the variation in the ability of the patient to describe symptoms accurately and in the interpretation of the patient's statements by the examiner. In order to obtain data which could be weighed objectively to evaluate the patients classified as asymptomatic, studies of the circulation were performed. By examining the records and questioning these patients, we have attempted to find out the type and amount of work they are actually doing at present and what brought them to seek medical care.

Analysis of Presenting Complaints. Not one of the 45 patients in the asymptomatic group sought medical care because of symptoms relating to the cardiovascular system. Of the 13 patients in Group II there was also none whose cardiac symptoms influenced him to seek medical care. As would be expected the patients in Group III sought medical care because of symptoms of cardiac insufficiency in practically all instances. However, even in this group there were 2 patients whose syphilis, and consequently whose cardiac disease, was first detected by the obtaining of a blood Wassermann as a routine measure, 1 of these being the father of a patient with juvenile paresis discovered in a family investigation. In the cases of the other 31, cardiac symptoms brought them to the doctors and the clinical diagnosis of aortic syphilis was the cause of their being referred to the syphilis clinic.

Combining the three groups of 91 patients with syphilitic aortic insufficiency, only 31 (34%) sought medical care because of symptoms referable to the heart; 53 (58%) consulted physicians or came to the hospital because of complaints entirely unrelated to the cardiovascular system; and 7 (8%) did not seek medical care at all but were discovered to have syphilis by the routine testing of donors, families of known syphilitics, and applicants for employment. The presenting complaint or disease causing the complaint for each member of Groups I and II are listed in Table 4.

TABLE 4.—COMPLAINTS OR PATHOLOGIC CONDITION RESPONSIBLE FOR THE COMPLAINTS WHICH BROUGHT PATIENTS IN GROUPS I AND II TO SEEK MEDICAL CARE.

Presenting complaint or cause of complaint.	Number of patients.	
	Group I (asymptomatic).	Group II (symptoms on questioning only).
Headaches and nervousness	4	0
Arthritis	3	1
Tabetic pains	3	0
Peptic ulcer	3	2
Uterine bleeding	3	0
Dizziness	0	2
Voluntary donor	2	0
Miscellaneous*	27	7

* The following were presenting symptoms in 1 case each: (Group I) Upper respiratory infection, trichiniasis, nausea, skin rash, failing vision, attacks of unconsciousness, bronchiectasis, Malta fever, fractured vertebrae, infected finger, hernia repair, renal colic, urethral discharge, carcinoma of bladder, epididymitis, prostatic hypertrophy, pyelitis, renal tuberculosis, vaginal discharge, menopausal syndrome, uterine fibroid, tinnitus and deafness, cataract, preemployment examination, family investigation, routine serology by private physician and by Life Extension Institute; (Group II) Failing vision, unconsciousness, lobar pneumonia, cholelithiasis, gastritis, fractured tibia, routine serology in jail.

Of the entire group of 91 with syphilitic aortic regurgitation, 47 patients were available for clinical investigation. Twenty-three patients were from Group I, 7 from Group II, and 17 from Group III. It must be emphasized that the classification of the individual

patients into the various groups was done solely on the basis of the examiner's judgment at the time of the initial examination in the clinic. Some changes in the status of individual patients have occurred since their original classification, but these have been few, so that in general the circulatory studies serve as an objective check on the classification.

Data on the amount of work that the patients are actually doing are included only for this group of 47 who were the subjects of the clinical studies as it was felt that, in this particular, only the most recent information would be of any value.

Sixteen of the 23 (Group I) patients have jobs at present. An additional 4 are housewives who do all their own housework, and the remaining 3 are men who are unable to secure employment. None of these patients has modified his activity in any way, either at work or at home, because of his cardiac disease.

Two of the 7 patients studied in Group II are gainfully employed, 1 is able to work but cannot find a job. An additional 2 are housewives who do all their own work. One is unable to work because of central nervous system syphilis, and 1 because of a chronic osteomyelitis.

In Group III there are 3 patients who are employed, an additional 2 who do all their own housework, 4 who help with housework but whose activity is modified because of the heart disease, and 8 who are unable to do any work at all because of cardiac symptoms. The type and hours of work are recorded in Table 5.

Measurements of the Circulation. Measurements of the vital capacity, arm-to-tongue circulation time and venous pressure were obtained on the 47 patients in the three groups.

Decholin was used for the arm-to-tongue circulation time. Five cubic centimeters of a 20% solution were injected rapidly through an 18-gauge needle into an antecubital vein while the individual was lying quietly in the supine position. The time was recorded from the beginning of the injection until the first perception of the bitter taste by the patient. All tests were repeated within 2 minutes as a check. The value recorded is an average of the two readings. In a few instances when an antecubital vein was not available, more distal arm veins were entered with a smaller needle (20-gauge). In every one of these cases, however, the circulation time was well within normal limits. Tarr and his associates¹⁹ found that the normal value for the circulation time by this method ranged between 10 and 16 seconds. Stewart and Watson¹⁷ found that the individual estimations in a group of normal subjects tested by this method ranged from 10.4 to 17 seconds. The venous pressure was measured by the direct method, using an antecubital vein placed on a level with the right auricle. An L-shaped glass tube attached to a 3-way stopcock, syringe and an 18-gauge needle were used. The apparatus was filled with sterile normal saline solution before the veni-

puncture and the direct pressure readings recorded. Normal values for this method are up to 120 mm. saline. Measurements on a 2-meter Roentgen ray film of the greatest transverse cardiac diameter, the internal thoracic diameter just above the diaphragm, and calculations of the cardiothoracic ratio were made. The vital capacity was measured in the usual fashion with the subject in a sitting position, recorded in cubic centimeters and calculated in per cent of normal. Normal values were taken from those of West,²⁰ namely 2.5 liters per square meter of surface area for men and 2 liters per square meter for women.

TABLE 5.—TYPE AND APPROXIMATE HOURS OF WORK PERFORMED BY THE 45 PATIENTS STUDIED.

	Type of work.	Hours (per day).
<i>Group I—(Asymptomatic).</i>		
J. Mc.	Distributor for bottled gas company	9
B. F.	Head matron, department store	8
J. F.	Apartment house superintendent	9
M. F.	Cook	8
M. G.	Waiter	8
S. K.	Janitor for 44-family building	15
C. K.	Machine shop	8
J. M.	Chauffeur	10-16
A. R.	Furrier	10
M. V.	Cabinet maker	12-16
M. D.	Taxi driver	10
B. A.	Cigar maker (2 days a week; also does own housework)	10
S. M.	Seamstress (also helps with housework)	6
M. Z.	Salesman	5-6
B. J.	Nursemaid (2 children)	Full time
H. J.	Nursemaid (4 children)	Full time
B. F.	Housewife—housework for 6 people	Full time
B. G.	Housewife—housework for 2 people	
C. M.	Housewife—housework for 2 people	
A. K.	Housewife—housework for 2 people	
J. E.	Unemployed—able to work	
A. W.	Unemployed—able to work	
A. I.	Domestic servant	Full time
<i>Group II—(Symptoms on Questioning Only).</i>		
L. L.	Waiter	6
H. J.	Decorator	7
G. F.	Housewife—housework for 2	
F. W.	Housewife—housework for 2	
F. K.	Unemployed—able to work	
J. B.	Unemployed—unable to work because of CNS syphilis	
J. Mc.	Unemployed—unable to work because of osteomyelitis	
<i>Group III—(Symptomatic).*</i>		
W. W.	Bricklayer (3 days a week)	8
S. W.	Salesman (4 days a week)	8
M. B.	Bar tender (1 day a week)	9
M. M.	Housework for 2 people	
R. K.	Housework for 3 people	

* Of the remaining 12 Group III patients, 4 are able to assist with housework but cannot work all day, and 8 are unable to work at all.

Data. The data for the patients of all three groups are recorded in Table 6. The correlation between the clinical impression of the state of the circulation and the data obtained from these tests was

quite close. Closest correlation was found, as would be expected, in the circulation times and cardiothoracic ratios. The vital capacity readings can be said to show only a general relationship to the presence or absence of symptoms. This is in accord with the observations of Harrison.⁷

TABLE 6.
Vital capacity.

Name.	Circ. time, sec.	Venous pressure, mm. saline.	Cc.	% of nor- mal.	Cardio- thoracic ratio.	Heart width, cm.	Aortic dilata- tion.*	Blood pressure.
<i>Group I (Asymptomatic).</i>								
B. J.	10.2	79	2350	78	42	11.2	0	150/85
M. F.	10.6	70	2400	74	46	13	0	150/82
J. F.	10.7	60	2000	74	46	10.2	0	160/80
S. M.	11.4	..	2700	90	46	12	0	140/80
M. I.	11.9	81	2300	66	50	13	+	130/90
E. G.	12.0	100	2300	80	43	12.4	0	150/70
H. J.	12.1	50	2000	74	69	16	0	170/90
J. M.	12.5	70	3800	90	0	180/90
A. R.	12.6	100	3400	72	138/96
B. F.	13.9	95	2000	66	56	13.5	+	270/145
A. K.	14	..	2000	66	53	12.9	0	155/80
B. A.	14	90	2800	80	49	15.5	+	190/54
M. D.	14.5	94	3500	80	42	11.5	0	130/60
A. W.	15	92	3150	85	46	14.5	+	168/64
M. Z.	15.8	115	2500	60	0	190/80
H. M.	16.6	80	2400	56	210/70
D. F.	16.9	44	1900	54	55	15	0	190/90
M. V.	17.2	68	2900	62	49	14	0	125/60
S. K.	17.3	88	3400	94	52	14.5	0	140/70
S. E.	18.1	51	3350	80	42	11	+	170/90
M. Mc.	18.4	88	1400	38	55	15	+	162/82
M. G.	18.5	70	2200	55	54	13.9	0	180/90
C. K.	..	90	3500	80	42	15.5	+	158/80
<i>Group II (Symptoms on Questioning Only).</i>								
F. K.	12.2	103	3600	84	58	16.2	0	170/70
G. F.	12.7	..	2000	70	43	10.4	+	188/86
H. J.	13.6	37	2500	75	49	12	0	135/60
F. W.	14.4	78	1600	45	58	17	+	214/78
L. L.	15.6	50	2700	78	47	13.3	0	208/80
J. B.	22.4	65	3100	76	50	16	0	170/65
J. Mc.	29.8	135	1850	42	67	17.5	+	200/65
<i>Group III (Symptomatic).</i>								
S. W.	12.6	90	2200	46	49	14.7	+	140/50
W. W.	13	54	3800	83	43	13.5	0	150/55
G. E.	13.7	124	2000	61	53	14	0	190/94
R. K.	14.1	102	2700	90	42	10.5	0	180/90
C. B.	14.5	98	2000	45	51	14	0	190/70
J. G.	14.7	85	2800	63	55	16	0	160/60
A. C.	14.9	82	2300	81	55	13.2	+	180/60
A. N.	16.3	99	1750	58	55	13.5	0	212/110
M. B.	16.6	97	2600	53	53	17	+	145/60
M. Mc.	17.9	130	2000	76	58	14.8	+	158/32
G. L.	19.7	86	2700	72	55	15.4	+	150/40
G. W.	22.5	50	2000	70	60	13.3	0	170/45
J. K.	22.8	117	2500	56	165/50
J. Mc.	23.8	82	2400	59	68	19	+	220/90
J. P.	24.6	72	2500	64	57	17.3	0	194/50
F. N.	28.2	52	2000	41	56	16.8	+	140/70
J. M.	29.8	53	3000	65	57	18.2	+	170/15

* By Roentgen ray.

There were only 5 patients of the 23 in the asymptomatic group who had circulation times higher than 17 seconds, and the extreme was 18.5 seconds. The venous pressure determinations were all within normal limits, ranging from 44 to 115 mm. of saline. In 7 patients the cardiothoracic ratio, calculated from the measurements of the Roentgen ray, was more than 50 with an extreme of 69.

In Group II, of 7 patients studied the circulation time was normal in 5, markedly prolonged in 2. One of these 2 patients has paresis and cannot be relied upon regarding symptoms. The other patient is a cripple because of a chronic osteomyelitis of the tibia and would probably have symptoms if he were capable of any very great activity. The venous pressure determinations were normal in all except the latter patient mentioned above. The cardiothoracic ratio was increased in 3 of the 7.

Of the 17 patients in Group III, there were 8 with prolongation of the circulation time, 2 with increased venous pressure and 13 with a cardiothoracic ratio of greater than 50. It is noteworthy that of the patients in this group in the greatest degree of failure, none had increased venous pressure. These patients were all receiving digitalis. There were only 2 patients in this group (W. W. and S. W.) who showed normal values for all three examinations. Both of these would be classified as completely asymptomatic on the basis of their present status but are included in Group III because their original complaints were cardiac. One (S. W.), following therapeutic malaria in 1934, developed congestive failure which disappeared promptly and has not returned. He is working as a bricklayer at present. The other (W. W.) originally sought medical care because of attacks of substernal pain unrelated to exertion which completely disappeared following antisyphilitic therapy. He is working as a salesman at present.

Combining the data for all three groups: of 47 patients there were 15 with abnormally prolonged circulation times, 3 with increased venous pressure, and 23 with a cardiothoracic ratio of more than 50.

Roentgenologic Evidence of Aortic Dilatation. There is a great variety of opinion as to the significance of the presence or absence of aortic widening as demonstrated by Roentgen ray in the diagnosis of aortic syphilis.^{6,8,16,18} No universally accepted method of measuring the aorta is available.¹⁸ The subjective element in estimations by fluoroscopy is a great variable, and as has been recently emphasized¹³ the part of the aorta most frequently involved by syphilis, the root, is not visible for the first 1.5 to 2 cm. on plates taken by conventional techniques. Because these pitfalls exist in the use of the Roentgen ray or fluoroscope as an aid to establishing the presence of syphilis in the aorta, it is of interest to see what the roentgenologic findings are in this group in whom the presence of aortic syphilis is known.

Estimations of aortic width of these patients were made on the basis of left oblique and P-A plates supplemented in the majority of instances by fluoroscopy. Eighty-seven of the 91 patients with aortic regurgitation were examined by these methods. The aortas were considered to be widened in 50 (57%) of these and in 37 (43%) there was no evidence of aortic dilatation.

Wassermann Reactions. Because there is such a wide range (65% to 95%) in the reported incidence of positive Wassermann reactions in patients with syphilitic aortic insufficiency,^{4,9,14,24} we have included our data for the entire 91 patients.

The blood Wassermann reaction was positive in 78 (85%) patients. In 8 other patients (9%) the reaction was doubtful or negative but there was a history of a previous positive test and previous anti-syphilitic therapy. In 4 patients (4.3%) the Wassermann reaction was doubtful (1+ to 3+) with no history of previously positive tests (2 of these patients showed positive (4+) Kline and Kahn flocculation tests). One patient had a negative blood Wassermann but the spinal fluid Wassermann reaction was positive. Thus, in every one of the 91 patients there was definite serologic evidence of syphilis or a history of such evidence.

These patients represent a group, a majority of whom would not have been known to have aortic syphilis had not the presence of the syphilis been discovered first, either by routine testing or because of clinical evidence of neurosyphilis. Therefore, there is a possible source of error in estimating the incidence of positive serologic reactions in such material. For comparison, data on this point were obtained in another group of patients, namely from the records of all patients admitted to the in-patient service of this hospital since September 1, 1932, in whom a clinical or postmortem diagnosis of aortic valvular syphilis had been made. All patients in the clinic series reviewed above are excluded from this group. These patients, therefore, were not examined simply because they were known to have syphilis. The serologic data were obtained from the routine serologies taken on all patients admitted to the in-patient service.

Of a total of 44 cases, 32 had positive (4+) blood Wassermann reactions, 6 had doubtful (1+ to 3+) reactions but gave a history of having had a previous positive reaction with treatment, and 1 had an anticomplementary reaction but had a positive spinal fluid Wassermann. In 2 patients, a doubtful reaction (1+ to 3+) in the absence of any history was obtained and in 3 others (6%) there was no serologic or collateral evidence of syphilis other than the presumably insignificant finding of doubtful (1+ to 3+) Kline flocculation tests.

These three groups of patients combined (135) represent all the patients with syphilitic aortic insufficiency uncomplicated by aneurysm, seen in any department of this hospital during the 8½-year period from September 1, 1932, to April 1, 1941. Thus, there were

only 3 patients (2%) of the entire 135 who showed neither serologic nor historical evidence of syphilis.

TABLE 7.—INCIDENCE OF POSITIVE WASSERMANN REACTIONS IN 135 PATIENTS WITH SYPHILITIC AORTIC REGURGITATION.

Total	No. of patients.	Per cent.
Total	135	
Positive blood Wassermanns	110	81.5
Doubtful (1+—3+) blood Wassermanns but history of previous positive Wassermann and therapy	14	10.4
Negative blood Wassermann but positive spinal fluid Wassermann	2	1.5
Doubtful (1+—3+) blood Wassermann with no history of previous positive or therapy	6	4.4
Negative Wassermann, no history of previous positive Wassermann or of therapy	3	2.2

Discussion. Examination of this material shows that the usually accepted clinical concept of syphilitic aortic insufficiency represents only the end stage of the condition. There is a clinically recognizable stage which may be reckoned in terms of years during which the patient has no symptoms referable to the heart and is able to carry on normal activity. That such a stage exists is, of course, well known. However, it has seemed to us that the fact has never been sufficiently emphasized that in a large group of syphilitics, asymptomatic aortic valvular disease is actually more common than the symptomatic form. Obviously patients in this phase of the disease would not be seen in any numbers in in-patient services or cardiac clinics as they are completely unaware of their need for medical care. The list of chief complaints of the 58 patients in Groups I and II shows a great variety of symptoms none of which would serve to direct attention to the heart. For many of these complaints the patients would be handled in special clinics in which an examination of the heart is not done routinely. It is only by the examination of all known syphilitics and the unearthing of previously unknown symptomless syphilis by routine serologic testing that patients with aortic regurgitation in the asymptomatic phase will be discovered. With the recent greatly increased use of routine serologic testing as a case-finding method, many more syphilitics who did not realize the fact of their infection are being found so that the recognition of this type of valvular syphilis is becoming more important.

Prognostic data, based as they are on the course following the onset of symptoms of failure, are valueless in this type of case. The information to be sought is how long these patients survive from the time the valvular disease is first detectable.

As there is an increasing body of evidence that specific antisypilitic therapy, including the judicious use of arsenicals, prolongs life in cardiovascular syphilis, the recognition of this asymptomatic

phase of aortic valvular syphilis is of therapeutic value. For, although the active syphilitic process of the aorta is predominantly in the media and the vasa vasorum of the adventitia, the ultimate anatomic change causing the altered physiologic response is in the intima and the valve leaflets. In a recent publication on this subject, Wilens²³ has stated, "Thus the weight of evidence seems to indicate that the cusps are secondarily and passively altered in much the same fashion as is the intima elsewhere. Primary specific inflammatory changes of syphilitic aortitis involving the intima directly are perhaps just as rare as similar changes in the leaflets of the aortic valve, the superior portions of which, at least, are but appendages of the inner layer of the aorta." As these all-important intimal and valvular changes are largely non-inflammatory, they are presumably unaffected by therapy. The rôle of specific therapy here is to check the gummatous process in the underlying aorta before the passive alterations of the valve have become too far advanced. There is, of course, no exact clinical method for measuring how far the underlying aortitis has progressed. However, it is reasonable to assume that these asymptomatic patients with the early diastolic murmurs have a less advanced stage of the inflammatory process in the aortic wall and hence can receive maximum benefit from specific therapy.

With but few exceptions the living patients in all three groups are receiving continuous antisypilitic therapy, including courses of neoarsphenamine administered cautiously. The period of follow-up is too short to attempt to evaluate the effects of the therapy at this time. We can say, however, that we have seen none of the reported harmful effects of therapy such as the therapeutic paradox or Herxheimer reactions around the coronary ostia.^{11,22}

The circulatory studies in most instances conformed closely to the clinical evaluation of the status of the individual patients. The measurements served as collateral evidence of the good functional capacity of the circulation of the members of the asymptomatic group. As would be expected the earliest objective change after the development of the diastolic murmur was the alteration of the cardiothoracic ratio. The fact that the aortas of the 37 (43%) of a total of 87 patients with syphilitic aortic regurgitation were considered to be normal in width by Roentgen ray and fluoroscopy emphasizes the inadequacy of the Roentgen ray as a means of excluding the presence of aortic syphilis. In making the decision between treating or not treating a middle-aged patient with apparently latent syphilis, too great reliance should not be placed on the normal appearance of the aorta by Roentgen ray. This fact alone serves as a justification for the policy of completely reexamining all syphilitic patients at regular intervals.

Analysis of the specificity of the Wassermann reaction shows that in only 3 patients (2.2%) of a total of 135 with syphilitic aortic

insufficiency was the blood Wassermann reaction negative in the absence of a history of previous treatment for syphilis. The discrepancy between these figures and those quoted in the literature is partially due to the marked increase in the sensitivity of the Wassermann reaction since its introduction 34 years ago. Even now the sensitivity of the test varies between different laboratories depending upon the technique used.¹⁰ While no exact figures are available in the literature, an estimate has been made that the test commonly employed during the decade 1910-1920 gave positive results in 70% to 80% of all patients with secondary syphilis,^{2a} whereas with modern techniques the Wassermann reaction is almost 100% sensitive in syphilis of this type.^{2b} Obviously, analyses of series of cases dating back to the twenties or earlier will give an erroneous impression as to the incidence of positive Wassermanns among cardiovascular syphilitics today.

Summary.—1. In a $4\frac{1}{2}$ -year period in the syphilis division of the medical clinics of the New York Hospital, the incidence of syphilitic aortic insufficiency without aneurysm was 3.4% (91 of 2718).

2. One-half of these patients (49.5%) with aortic regurgitation denied any symptoms of cardiac insufficiency at the time of diagnosis.

3. Only 31 (34%) of the 91 patients sought medical care because of symptoms referable to the heart, 53 (58%) sought care for non-cardiac complaints, and 7 (8%) were brought under medical care by the routine serologic testing of supposedly well people.

4. Of 28 of these asymptomatic patients followed for more than 2 years, 2 have died of heart disease and only 2 have developed symptoms.

5. Circulatory studies (vital capacity, venous pressure, circulation time and roentgenoscopy) of 47 of these patients showed a close correlation with the clinical impression of their cardiac status.

6. The aortic width, as judged from Roentgen ray and fluoroscopy, was normal in 37 of 87 (43%) of these patients with aortic insufficiency.

7. In only 3 patients (2.2%) of a total of 135 with syphilitic aortic insufficiency was the blood Wassermann reaction negative in the absence of a history of previous antisyphilitic treatment.

Conclusions. Aortic insufficiency due to syphilis is present in a clinically recognizable form for a relatively lengthy period of time (2 to 10 years) before the development of symptoms.

This asymptomatic form of aortic valvular syphilis is encountered in approximately one-half of the patients with valvular syphilis.

Present-day prognostic data, based as they are on the course following the onset of symptoms of failure, are inapplicable to this large group of patients with cardiovascular syphilis.

There are no available data on the ultimate length of this asymp-

tomatic phase, but it appears from a study of our cases thus far that it can be measured in terms of years rather than months.

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PROLONGATION OF THE P-R INTERVAL IN PATIENTS WITH PAROXYSMAL AURICULAR FIBRILLATION AND FLUTTER FOLLOWING MYOCARDIAL INFARCTION.

By MAX J. KLAINER, M.D.,

ASSISTANT IN MEDICINE, BETH ISRAEL HOSPITAL,

AND

MARK D. ALTSCHULE, M.D.,

ASSOCIATE IN MEDICINE, HARVARD MEDICAL SCHOOL; ASSOCIATE VISITING PHYSICIAN
AND ASSOCIATE IN MEDICAL RESEARCH, BETH ISRAEL HOSPITAL,
BOSTON, MASS.

(From the Medical Research Laboratory, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.)

PAROXYSMAL auricular fibrillation and flutter are among the arrhythmias most commonly encountered in patients with coronary thrombosis. They have also been observed following ligation of a coronary artery in animals.³ The occurrence of an auricular arrhythmia during the course of myocardial infarction cannot be explained on an anatomical basis since the arteries involved and the infarct itself are always in the ventricular myocardium.

A considerable volume of evidence indicates that experimentally produced auricular fibrillation in animals is due at least in part to vagal activity.⁵ The activity of the vagus nerve recently has been implicated in the genesis of auricular fibrillation which occurs in patients with thyrotoxicosis¹⁰ and rheumatic heart disease.¹ It was

therefore of interest to study patients in whom auricular fibrillation occurred following myocardial infarction in order to determine the frequency of other changes in cardiac conduction which might be interpreted as due to increased vagal activity.

Material. The records of all patients were examined in whom paroxysmal auricular fibrillation or flutter first appeared soon after myocardial infarction. Only those with electrocardiographic evidence of auricular fibrillation or flutter within 12 days after a definitely diagnosed attack of cardiac infarction were included in this study. A few were eliminated because no records were made during the periods of normal rhythm, so that no comparative studies could be made. There remained 14 cases suitable for analysis.

Results. All patients exhibited changes in T waves and ST segments considered characteristic of infarction of the ventricle. In addition 9 of the 14 patients showed prolongation of the P-R interval on one or more occasions within a few days prior to or following the onset of auricular fibrillation. In one instance the P-R interval had been prolonged for several years previously. In all 9 instances the P-R interval varied considerably from day to day; in 8 of the 9 cases it decreased to within normal limits at one time or another. The occurrence of prolongation of the P-R interval and the onset and offset of auricular fibrillation were not related to medication or changes in physical signs such as cyanosis, collapse, or congestive failure.

Discussion. Less than 10% of 375 patients with acute coronary occlusion studied by Master *et al.*⁸ exhibited a P-R interval greater than .20 second. The fact that 9 of 14 cases or 64% of our patients with paroxysmal auricular fibrillation or flutter after coronary occlusion showed prolongation of the P-R interval, usually transitory, must therefore be considered significant. In the 5 patients who did not show prolonged P-R interval an average of less than four tracings were made during periods of normal rhythm as compared with an average of more than 8 in the other cases; the abnormally prolonged P-R interval may perhaps be found more frequently if electrocardiograms are taken more often. Master *et al.*⁸ observed paroxysmal auricular fibrillation in 2 patients with prolonged P-R intervals after coronary occlusion.

In 1937 Bruenn² and Keith⁶ showed that the prolonged P-R interval seen in acute rheumatic fever is due to increased vagal activity. It has been pointed out in another place¹ that such evidence of increased vagal activity is frequently found in patients with rheumatic heart disease in whom auricular fibrillation develops. Of interest likewise is the fact that repeated injections of acetyl- β -methyl choline in normal unanesthetized dogs gives rise either to auricular fibrillation or to partial heart block, the arrhythmia which will develop being entirely unpredictable.⁵ The sequence of events as revealed by electrocardiographic study in patients with auricular

fibrillation following coronary occlusion resembles that seen in dogs receiving repeated injections of acetyl- β -methyl choline.

The cause of the prolonged P-R interval seen in coronary artery disease has not yet been completely elucidated, although available evidence strongly suggests its functional origin. Master and his co-workers⁸ found no anatomical lesion to explain it; this is readily understandable since infarction of that portion of the myocardium containing the A-V node is infrequently found at postmortem examination. Moreover, these authors⁸ found that atropine shortened the P-R interval in 2 of 3 patients with prolongation of the P-R interval associated with cardiac infarction. Additional work in this regard is however necessary before the vagal origin of prolonged P-R intervals after myocardial infarction can be accepted as proved. Master *et al.*⁸ suggested that anoxemia might be a factor in causing a prolonged P-R interval after cardiac infarction. These authors, however, noted its frequent occurrence after the disappearance of evidences of anoxemia. In the present study anoxemia or shock could not be implicated as the factor responsible for the increase in P-R interval. Although prolongation of the P-R interval has been induced by anoxemia in animals^{7,9,11} and in man⁴ the degree of anoxemia necessary to produce this change is far greater than that observed in cases of heart disease.

The available data, though scanty, suggest that the prolonged P-R interval associated with cardiac infarction is probably the result of increased vagal activity. The occurrence of auricular fibrillation and flutter following infarction of the ventricle therefore becomes understandable since the rôle of vagal activity in production of auricular fibrillation and flutter in animals⁵ and in man in thyrotoxicosis,¹⁰ and rheumatic fever¹ has been pointed out. The origin of vagal impulses which may act on the heart and so give rise to auricular fibrillation following myocardial infarction will be the subject of another study.

Summary. 1. The frequent occurrence of auricular fibrillation and flutter following cardiac infarction cannot be explained as directly due to anatomical findings, since the latter lesions are almost always ventricular.

2. Sixty-four per cent of patients with paroxysmal auricular fibrillation and flutter due to cardiac infarction also have a variable but abnormally prolonged P-R interval within a few days of the onset of fibrillation.

3. Available evidence, though scanty, suggests that the prolonged P-R interval of cardiac infarction is probably due to increased vagal activity.

4. Since increased vagal activity appears to be one factor responsible for the occurrence of auricular fibrillation in general, the occurrence of this arrhythmia following ventricular infarction becomes understandable.

TABLE 1.—P-R INTERVAL AND OCCURRENCE OF AURICULAR FLUTTER AND FIBRILLATION AFTER CARDIAC INFARCTION.*

Days after infarction.	P-R interval.	Cardiac rate.	Days after infarction.	P-R interval.	Cardiac rate.
<i>Case 1.</i>			<i>Case 7</i>		
0	A.F.†	170	Before	.16	70
1	.20	65	3	.24	70
4	.16	60	4	.18	70
24	.24	65	5	A.F.	75
30	.22	65	<i>Case 8.</i>		
30	A.F.	140	1	A.F.	160
31	.18	65	2	A.Fl.	140
33	.22	70	4	.20	90
42	.18	60	14	.22	80
<i>Case 2.</i>			16	.20	80
0	.14	120	36	.24	70
3	.22	120	<i>Case 9.</i>		
4	A.F.	140	Before	.26	65
<i>Case 3.</i>			2	.28	85
6	.20	120	<i>Second infarction</i>		
7	A.F.	160	2	.16	120
12	.24	90	2	A.F.	120
<i>Case 4</i>			7	.28	55
Before	.16	80	11	.30	75
1	.22	100	<i>Case 10.</i>		
2	.20	90	4	.14	75
5	.18	90	11	.16	110
<i>Second infarction</i>			12	A.Fl.	150
0	A.F.	170	14	.16	90
5	A.F.	110	<i>Case 11.</i>		
15	.1	90	3	.16	100
36	.20	90	5	A.F.	170
<i>Case 5.</i>			20	.16	60
1	.14	120	<i>Case 12.</i>		
2	A.F.	180	3	.16	85
7	.16	90	5	A.F.	110
22	.24	90	8	.18	70
30	.16	70	<i>Case 13.</i>		
<i>Case 6.</i>			2	A.F.	140
5	.22	65	4	.18	75
7	.20	70	10	A.Fl.	160
<i>Second infarction</i>			<i>Case 14.</i>		
1	A.Fl.‡	150	1	.16	90
2	.20	90	6	A.F.	190
3	A.Fl.	160	9	.14	80
6	.22	80			
20	.20	80			

* A number of repetitive observations have been omitted for lack of space.

† Auricular fibrillation.

‡ Auricular flutter.

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A JUSTIFICATION FOR THE INCREASING USE OF ELECTROCARDIOGRAPHY IN HOSPITAL PRACTICE.

By ARTHUR J. GEIGER, M.D.,
ASSISTANT PROFESSOR OF MEDICINE,

MASSIMO CALABRESI, M.D.,*
RESEARCH FELLOW IN MEDICINE,

AND

LOREN F. BLANEY, M.D.,
ASSISTANT IN MEDICINE,
NEW HAVEN, CONN.

(From the Department of Internal Medicine, Yale University School of Medicine, and the Medical Service of the New Haven Hospital.)

DURING recent years there has been a steadily increasing demand for electrocardiography in the clinical study of patients in the New Haven Hospital and Dispensary. That the growing employment of this laboratory aid is only partly attributable to the increasing number of patients is shown by Table 1, which reveals that the ratio of electrocardiograms to the number of patients studied annually has been rising. Since approximately 75% of all electrocardiograms obtained have been on patients in the medical division of both hospital and dispensary, the figures for these may be more relevant and are included also in Table 1. It is evident that during the last 12 years the number of tracings taken on every 100 patients has more than doubled. In the same interval, mortality from heart disease in New Haven has risen slightly less than 20%. It is clear, therefore, that there has actually been a growing general use of electrocardiography in the elucidation of clinical problems.

TABLE 1.—ANNUAL RATIO OF ELECTROCARDIOGRAMS PER 100 PATIENTS.

Year	1920.	1930.	1931.	1932.	1933.	1934.	1935.	1936.	1937.	1938.	1939.	1940.
Electrocardiograms	319	340	375	548	465	585	627	873	882	1,017	1,369	1,693
All hospital patients	6,551	6,601	7,454	7,343	7,554	8,156	8,871	9,177	9,304	9,628	10,125	12,236
All dispensary patients	8,720	9,780	10,950	13,900	19,068	18,627	16,612	15,440	14,285	15,807	16,136	16,495
TOTAL ALL PATIENTS	15,271	16,381	18,404	21,243	26,622	26,783	25,483	24,617	23,589	25,435	26,261	28,731
Ratio of ECG's per 100 patients	2.08	2.08	2.04	2.58	1.75	2.18	2.47	3.55	3.75	4.00	5.21	5.83
Medical hospital patients	1,170	1,289	1,443	1,391	1,361	1,483	1,499	1,646	1,804	1,912	2,237	2,651
Medical dispensary patients	850	1,050	1,300	1,680	1,869	2,311	1,781	1,558	1,550	1,540	1,594	1,696
TOTAL MEDICAL PATIENTS	2,020	2,339	2,833	3,071	3,230	3,794	3,280	3,204	3,354	3,452	3,831	4,347
Ratio of ECG's per 100 patients	15.5	14.5	13.8	17.8	14.4	15.4	19.1	27.3	26.3	29.5	35.7	38.9

In the face of such a steadily increasing demand for a laboratory service in relation to the number of patients studied, it is pertinent to inquire whether the augmented laboratory output is being accomplished at a relative loss in clinical value for each 100 electrocardiograms made, to determine whether any data of importance are contributed by the added effort, and to consider whether such additional information justifies the increased cost and the heavier tax on the laboratory facilities and personnel.

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These considerations engaged our attention, and answers to the questions raised were sought by acquiring information under the following three headings:

1. The relation between increasing employment of electrocardiography and the proportion of normal and abnormal records obtained.
2. Estimation of the clinical value of a representative group of electrocardiograms during a year of small demand as compared with a year of large demand.
3. Investigation of the results of *routine* electrocardiograms taken on a large group of patients who would not otherwise have had the benefit of electrocardiographic study.

SECTION I. *Relation Between Increasing Use of Electrocardiography and Proportion of Normal and Abnormal Records Obtained.* All the electrocardiograms obtained during a 12-year period, totaling 9093 records, were divided into three groups as follows:

1. Normal group—including sinus arrhythmia, infrequent ectopic beats, and moderate bradycardia and tachycardia (heart rates between 50 and 120).
2. Abnormal group—all others, excluding those which showed only left axis deviation.
3. Group having left axis deviation, of all degrees, as the only abnormality.

Table 2 and Chart 1 show the total annual output of electrocardiograms from this laboratory for the last 12 years and the number of records that were normal, abnormal, and characterized by left axis deviation only. It is apparent that as electrocardiograms were obtained more and more generally, the proportion of abnormal tracing not only rose steadily but practically paralleled the increase in the total number of records for each year, while the figures representing normal records showed a much more gradual ascent.

TABLE 2.—RELATION BETWEEN INCREASING DEMAND FOR ELECTROCARDIOGRAMS AND PERCENTAGE OF NORMAL AND ABNORMAL RECORDS OBTAINED.

Year.	ECG's taken.	Normal (%)	Abnormal (%)	L.A.D. only (%)
1929	319	32.0	58.8	9.2
1930	340	24.7	65.6	9.7
1931	375	27.8	58.8	13.6
1932	548	33.4	58.0	8.6
1933	465	30.4	53.4	16.2
1934	585	29.6	59.8	10.6
1935	627	34.9	50.4	14.7
1936*	873	25.2	62.8	12.0
1937*	882	21.0	67.0	12.0
1938†	1017	21.5	68.6	9.9
1939‡	1369	24.2	65.2	10.6
1940‡	1693	20.3	69.5	10.2

* Precordial leads taken on about one-third of the patients in this year.

† Precordial leads taken on about two-thirds of patients in this year.

‡ Precordial leads taken routinely on all patients in this year.

Expressed numerically, 58.9% of the electrocardiograms were abnormal in the first 5 years of the 12-year period, while 66.6% were abnormal in the last 5 years. This considerable and unexpected divergence of the curves for the normal and abnormal groups in Chart 1 implies that the rapidly increasing utilization of electrocardiography has not been wasted upon patients without heart disease, and it suggests that perhaps an even greater use of electrocardiography might serve as an important case-finding method.

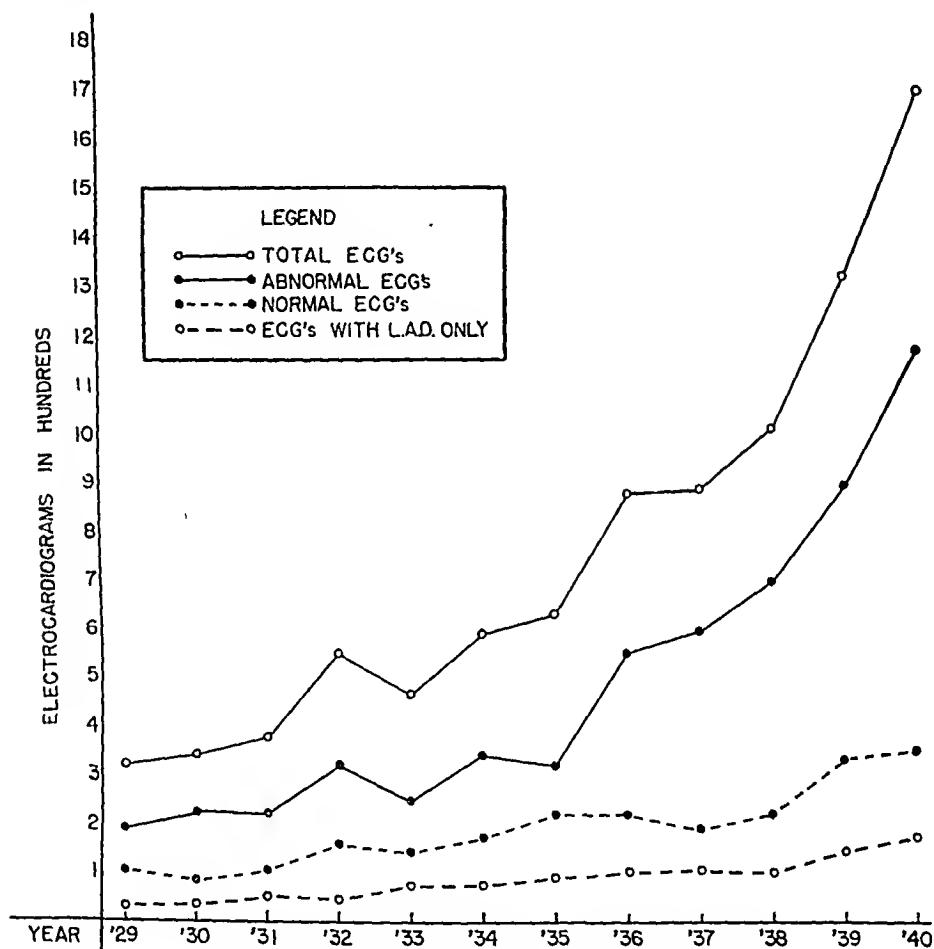


CHART 1.—Output of electrocardiograms since 1929.

Whether the augmented laboratory service actually contributed anything of real significance to the clinical study of patients seemed to be the next logical inquiry, for the proportion of normal to abnormal records is not strictly indicative of the clinical usefulness of the tracings.

SECTION II. *Estimation of the Clinical Value of Representative Groups of Electrocardiograms During a Year of Small Demand as Compared With a Year of Large Demand.* One hundred electrocardiograms were drawn from the laboratory files of 1934, a year of relatively low demand, and another hundred were taken from the

files of 1939, a year in which the demand was about twice as great as in 1934. The records selected were evenly distributed throughout each year, the quotient of the year's output divided by 100 being the interval between the serial numbers drawn: in this way we tried to avoid error arising from professional idiosyncrasies which might have prevailed in the ordering of the electrocardiograms at any period. Excluded from this study were tracings of patients who were already represented in this particular investigation by an electrocardiogram previously drawn.

Each electrocardiogram was then appraised as to its clinical value from a study of the case history. Each tracing was then classified as follows:

Class I: Records of decisive and exceptional significance in that they contributed distinctly new information to the clinical knowledge of a case.

Class II: Records with positive significance, either in confirming a clinical impression or definitely establishing a diagnosis which had been uncertain.

Class III: Records without positive significance whether normal or abnormal, and considered lacking in clinical helpfulness.

The classes were subdivided into two groups: Group A were normal electrocardiograms, and Group B were abnormal records. We sought also to determine whether in the year of greater call for electrocardiography there was evidence of less discriminating use of this laboratory aid. This was attempted by passing judgment on each record in Class III as to whether or not it appeared justified from a careful consideration of the clinical features. This was admittedly a somewhat arbitrary procedure, yet the independent deliberations of each of the three authors resulted in unanimity of opinion in all but a very few cases.

The basis of classification of the electrocardiograms may be clearer from the following examples of actual cases:

CLASS I, *Group A*. A middle-aged man was ill with typical clinical features of coronary thrombosis. Serial ECG's, of which the one considered here was the first, were all normal, and rendered this diagnosis untenable. This led to a suspicion of dissecting aneurysm which was finally diagnosed.

Group B. An elderly man under study for sudden severe headache and gastro-intestinal disturbance followed by dyspnea had a "routine" ECG which unexpectedly showed signs of acute myocardial infarction (with typical evolution of T-wave abnormalities in subsequent serial records).

CLASS II, *Group A*. An old woman with a history vaguely suggesting coronary thrombosis had a normal ECG, which was regarded as helpful in excluding the improbable diagnosis.

Group B. One 35-year-old man with a history suggesting coronary thrombosis had an ECG showing abnormalities compatible with but not typical of myocardial infarction. Another older patient with a similar history had classical ECG changes for anterior apical myocardial infarction. Both records supported the clinical impression and were therefore regarded as helpful.

CLASS III, Group A (justified). A middle-aged man with hypertension was suspected of having heart disease on this basis but definite evidence was lacking. ECG also was normal, therefore not positively helpful, yet thought to be justified.

Group A (unjustified). A young man with gigantism and psychoneurosis with respiratory symptoms, palpitation, and precordial discomfort had no abnormal cardiovascular findings and an ECG was normal. A second ECG, drawn in this study, was the same as the first, therefore considered unhelpful, and deemed unjustified since there were no new indications for its being repeated.

Group B (justified). A middle-aged woman with hypertension had been under treatment with digitalis for heart failure for several years. The ECG drawn in this study showed I-V block. Because similar findings had been disclosed 2 years before, this record was regarded as unhelpful yet justified at least because of the long interval between the examinations.

Group B (unjustified). An elderly man with known arteriosclerotic heart disease with auricular fibrillation. A first ECG showed the abnormal mechanism as well as left axis deviation and S-T and T changes of the variety due to digitalis. Another ECG, drawn in this study, was requested only a few days later without new indications, and the tracing was similar to the first. The second record was therefore deemed unhelpful and unjustified.

TABLE 3.—EVALUATION OF ELECTROCARDIOGRAMS IN A YEAR OF SMALL DEMAND AND A YEAR OF LARGE DEMAND.

	1934. 100 ECG's.	1939. 100 ECG's.
Class I (diagnostic*):		
Group A—Unexpectedly normal	0	2
Group B—Unexpectedly abnormal	16	12
Total	16	14
Class II (helpful):		
Group A—Normal	5	7
Group B—Abnormal	34	40
Total	39	47
Class III (unhelpful):		
Group A—Normal	14	20
Group B—Abnormal	31	19
Total	45	39

* Diagnostic in sense that unexpectedly new clinical data of importance resulted.

It is acknowledged that the two samples of 100 records are too small to permit statistical treatment, but the analysis as summarized in Tables 3 and 4 reveals interesting trends.

It is notable that in 1939, when electrocardiography was used about twice as frequently as in 1934, the percentage of insignificant or unhelpful records (Class III) was smaller, while the percentage of clinically helpful records (Classes I and II) was definitely larger (Table 3). Moreover, there were only about half as many seemingly unjustified records in the year of greater demand (Table 4). If one grants the liberal view that all of the Class I and II records were justified, then 85% of the tracings in 1934 and 92% in 1939 fall in this category. The actual differences in support of these observations are small, but the trend in the direction indicated, rather than

the opposite one, seems to us convincing evidence that the greater volume of work in the latter year was profitably expended.

That the greater clinical value of the records in 1939 was not due in any important respect to the routine employment of a precordial lead in this year was excluded by a specific inquiry which revealed that among the 100 electrocardiograms, of which 71 were abnormal, there were only 3 in which the interpretation of abnormality was dependent primarily or entirely on changes occurring in Lead IV-F.

TABLE 4.—JUSTIFICATION OF CLASS III (UNHELPFUL) ELECTROCARDIOGRAMS DURING A YEAR OF SMALL DEMAND AND A YEAR OF LARGE DEMAND.

Year.	Group.	Justified.	Unjustified.
1934 (45 ECG's)	A (normal)	10	4
	B (abnormal)	20	11
	Total	30	15
1939 (39 ECG's)	A (normal)	17	3
	B (abnormal)	14	5
	Total	31	8

SECTION III. *Inquiry Into the Value of Routine Electrocardiography.* We proceeded to investigate whether a significant amount of cardiac abnormality was being overlooked through the practice of obtaining electrocardiograms only when they seemed clinically indicated to the staff. We therefore undertook the following experiment.

Electrocardiographic observations were made on 300 patients from all divisions of the New Haven Hospital and 100 patients from the medical clinic of the New Haven Dispensary. All were patients for whom electrocardiograms were *not* requested in the ordinary course of the clinical study. Selection was exercised only in that subjects less than 13 years old were not included. In the interests of economy of materials and time most of these examinations were made with an amplifier type electrocardiograph whose galvanometer deflections were observed directly on a slowly-moving fluoroscopic lag-screen belt illuminated with horizontal millimeter lines and vertical 0.1 second time subdivisions.* The accuracy of these observations was verified by obtaining a conventional electrocardiographic record whenever there was doubt as to whether the measurement or character of any feature was within normal limits, and the interpretations of such permanent records were then compared with our notes based on the direct visual method; only a very few minor discrepancies were encountered. Electrocardiograms of the three usual limb leads and precordial Lead IV-F were studied.

In order to avoid influencing the professional house and attending staffs in their ordering of electrocardiograms on patients in the hospital, the investigation was done surreptitiously, usually over

* Sanborn cardiette and cardioscope.

week-ends, and information acquired by us was not divulged until the study was completed. We discarded and made substitutions for cases in which electrocardiograms were subsequently formally requested during the patient's hospitalization. In performing the 100 examinations in the out-patient clinic, only new patients were taken, they were chosen at random, and the observations were made early in the morning while the patients were awaiting the opening of the clinic. The case history pertaining to each of the 400 electrocardiograms was later searched for data and opinions bearing on the presence or absence of cardiovascular disease.

These examinations were conducted sporadically over a period of 9 months, chiefly in May and November, so that seasonal factors concerned in the type of cases admitted were partly controlled. During this time there were several changes in professional staff, and personal factors which might influence the frequency of calling for electrocardiographic aid were thus minimized.

TABLE 5.—ABNORMALITIES ENCOUNTERED AMONG 400 UNREQUESTED ROUTINE ELECTROCARDIOGRAMS.

Age group	13-29.	30-39.	40-49.	50-59.	60-69.	70+.	Total.	13-35.	36-49.	50+.
Number of ECG's	113	67	73	67	54	26	400	151	102	147
Normal ECG's	93	41	36	16	20	7	213	120	50	43
Moderate L.A.D.	3	15	19	23	12	6	78	11	26	41
Abnormal ECG's	17	11	18	28	22	13	109	20	26	63
	15.0%	16.4%	24.7%	41.8%	40.3%	50%	27.2%	13.2%	25.5%	42.9%
A-V block	1		1	1			3	1	1	1
I-V block			3	2	4	2	11		3	8
L.A.D. (marked)				1	2		3			3
R.A.D.	1			2			3	1		2
Abnormal QRS ₁	1	1	2	1	2		7	1	3	3
Low voltage	5	5	3	5	4		22	6	7	9
Abnormal S-T	1			1			2	1		1
T ₁ abnormally low		1					1		1	
T ₁ flat, inverted				2		1	3			3
T ₂ inverted, diphasic				1		1	2			2
T ₃ deeply inverted	1						1	1		
T ₄ inverted, diphasic	3	2	2	1	2	1	11	5	2	4
T abnormal in 2 leads or more	4	2	7	11	8	8	40	4	9	27

Each ECG is represented by the single most important abnormality it presented.

ECG abnormalities were established by the following: P-R interval in excess of 0.20 second. QRS duration in excess of 0.10 second. QRS amplitude not exceeding 0.5 mv. over all in the limb leads. Q wave in Lead IV-F more than 0.3 mv. in amplitude. R wave absent in Lead IV-F. Left axis deviation only when marked. Right axis deviation. S-T displacement of more than 0.1 mv. T-wave amplitude of less than 0.1 mv. in Leads I or II. T-wave inversion or diphasia in Leads I, II, and IV-F. T-wave inversion of unusual depth (5 mv.) in Lead III (one instance).

Not included among ECG abnormalities were the following: P-wave deformities. Very slight slurring of QRS. Low voltage of QRS in Lead IV-F only. Prominent Q wave in Lead III. Isoelectric T wave in Lead IV-F.

The results of this inquiry are summarized in Tables 5 and 6, from which it is seen that while 109 (27.2%) of the electrocardiograms were abnormal, some abnormality might have been expected in 60 (15%), but was an entirely unexpected finding in 49 (12.2%) of the patients examined. No patient was included in the "unexpectedly abnormal" group whose blood pressure exceeded 150 systolic or 95 diastolic. Moreover, if any detail in the recent history or physical findings had a possible cardiac implication the record was excluded from this group. Even after eliminating 22 cases

showing only low voltage (a net QRS amplitude not exceeding 5 mm. in the limb leads), and an instance of right axis deviation in a young woman, since these may not always establish organic disease of the heart, there were still 86 (21.5%) of the 400 examinations that revealed changes which are usually considered definitely abnormal, and of these 31 (7.8%) were unexpected. Furthermore, it is worth emphasizing that while the number of abnormal electrocardiograms in this group cannot easily be made smaller (see Discussion), there are several possibilities that it might actually be larger. Thus, although no borderline records are included in the group and even tracings with left axis deviation of moderate degree were excluded, some of these may well imply cardiac abnormalities in certain of our patients. Also, we ignored Q-T measurements entirely, yet there is evidence that prolongation of this interval beyond certain definite limits may indicate cardiac abnormality.¹ Moreover, in these *single* electrocardiographic examinations we may have overlooked the pathologic significance of records whose features were within normal or borderline limits, yet which possessed changes indicative of cardiovascular abnormality that would have been evident from serial studies. The importance of serial changes, even when slight, is well known⁷ and has been abundantly confirmed in our experience.⁴ Finally, a few cases were excluded from the "unexpectedly abnormal" group on the basis of a single blood pressure determination in which either a systolic or a diastolic reading exceeded our established limits but did not necessarily prove the existence of true hypertension or hypertensive heart disease. Even when the electrocardiographic abnormalities bore no conceivable relation to the abnormal clinical features, as in the case of a young woman with a craniopharyngioma and paroxysmal hypertension and with deviation of the electrical axis to the right, our convenient but conservative rule obliged inclusion of the case in the "expectedly abnormal" group.

TABLE 6.—EXPECTANCY AND FINDINGS OF NORMAL AND ABNORMAL ELECTROCARDIOGRAMS AMONG 400 UNREQUESTED ROUTINE RECORDS.*

Age group:	13- 29.	30- 39.	40- 49.	50- 59.	60- 69.	70+.	Total.	13- 35.	36- 49.	50+.
Expected normals . . .	100	61	51	33	22	10	277	135	77	65
Actual normals . . .	87	37	28	13	15	4	184	111	41	32
Abnormals . . .	11	10	13	9	3	3	49	14	21	15
Borderline . . .	2	14	10	11	4	3	44	10	16	18
Expected abnormals . .	13	6	22	34	32	16	123	16	25	82
Actual abnormals . .	6	1	5	19	19	10	60	6	6	48
Borderline . . .	1	1	9	12	8	3	34	1	10	23
Normals . . .	6	4	8	3	5	3	29	9	9	11

* Expectancy based on clinical findings and impressions.

Another fact of particular interest which emerged from this study was that electrocardiographic abnormalities occurred in 15% of the

subjects less than 30 years of age whose histories, physical signs, and clinical impressions gave no suggestion of cardiovascular disease. The relatively high incidence of abnormalities in the tracings among the elderly patients, even in the absence of other clinical evidence of heart disease, was perhaps to have been expected and has recently been emphasized by others also.^{5,6} In the younger age groups, however, these findings came as a surprise.

Because of the possible bearing of these observations on the judgment of physical fitness of men called to arms under the Selective Service Act, the age groups were recast to show the results among subjects through the draft age, as compared with middle-aged and elderly groups. Definitely abnormal electrocardiograms occurred in 13.2% of the youngest group without other clinical evidence of heart disease; if the borderline feature of left axis deviation is included, 20.5% of the group within the draft age were not normal. Since these observations are confined to a population made up of patients they are not necessarily applicable to the general population.

It is pertinent to the subject of routine electrocardiography to refer briefly to unpublished observations, carried out previously in this laboratory by A. D. Chidsey,² on electrocardiographic abnormalities encountered in the examination of patients with acute infectious diseases. Fifty subjects suffering chiefly from pneumonia, scarlet fever, and acute tonsillitis and pharyngitis, were selected for study because they had no history or physical signs of cardiac or vascular disease, were free from hypertension, and had received no drugs like digitalis or quinidine. Electrocardiograms, including the three limb leads and precordial Lead IV-F, were taken at 4- or 5-day intervals both at the height of the illnesses and during convalescence. In 22 of the patients (44% of the group) electrocardiograms that were judged either probably or definitely abnormal were obtained. Fifteen of the patients (30% of the group) exhibited definite abnormalities, either RS-T and T changes or delayed A-V conduction, which in all but one instance were transient or changing during the serial studies. A descriptive tabulation of this group of cases is presented in Table 7 (Chidsey's Table 4). Since the average age of these 15 patients was 25.6 years, of whom the 2 oldest were 42 and 43 years of age, respectively, not even asymptomatic coronary sclerosis can be invoked in explanation for the observed abnormalities, and it is believed that the serial changes indicated an acute myocardial involvement that was not evident clinically.

Electrocardiography seemingly offers an important case-finding method in the field of cardiovascular disease even among the relatively young who have had the benefit of examination and study by two or more physicians under hospital conditions. It appears that the routine employment of this laboratory aid discloses a significant incidence of electrocardiographic abnormality beyond that which might be expected from other clinical evidences.

TABLE 7.—FIFTEEN CASES SHOWING DEFINITE ELECTROCARDIOGRAPHIC ANOMALIES.

Case No.	Sex, Age.	Diagnosis.	No. of ECG's.	EKG changes.
6	M 23	Virus (?) pneumonia	3	T wave low and flat in all leads reverted to normal.
23	M 42	Lobar pneumonia	4	T wave low and flat in Leads I and II and diphasic in IV-F reverted to normal; prolonged Q-T throughout.
24	M 18	Lobar pneumonia	5	T wave low and flat in all leads reverted to normal.
27	F 7	Scarlet fever	6	T wave in Lead IV-F changed from upright to inverted and returned to upright; P-R interval changed from normal to prolonged and returned to normal; prolonged Q-T throughout.
30	M 27	Lobar pneumonia	3	T wave low and flat in Leads I and II reverted to normal in Lead I.
31	F 43	Acute pharyngitis	3	T wave low and flat in Lead I returned to normal; T wave in Lead IV-F changed from upright to inversion to diphasic.
32	F 10	Scarlet fever	4	T wave low and flat in Lead II returned to normal; T wave in Lead IV-F changed from upright to inversion, to upright; prolonged Q-T throughout.
37	F 14	Peritonsillar abscess	3	T wave in Lead IV-F changed from low to inverted with a high S-T level and then to diphasic.
40	M 29	Scarlet fever	5	T wave in Lead I changed from normal to inverted with low S-T segment level and returned to normal; in Lead II changed from normal to low and flat, and returned to normal; in Lead IV-F changed from diphasic to inverted and returned to normal; prolonged Q-T in second record.
41	M 40	Peritonsillar abscess	3	Incomplete A-V block throughout; P-R interval 0.22 second.
42	F 24	Pneumonitis	2	T waves flat in Leads I and II with low S-T segment in Lead IV-F returned to normal.
45	M 19	Lobar pneumonia	5	T wave in Lead I flat and low returned to normal; T wave in Lead IV-F deeply inverted returned to upright; abnormal QRS in Lead IV-F throughout; prolonged Q-T throughout.
47	M 30	Lobar pneumonia	3	Incomplete A-V block throughout; P-R interval 0.22 to 0.26 second; T wave in Lead II low returned to normal, and in Lead IV-F diphasic returned to normal.
48	F 40	Erysipelas	4	Abnormally large and notched P waves in Leads II and III returned to normal.
49	M 18	Meningococcemia	3	T wave in Lead II low and flat with deeply inverted T wave in Lead III returned to normal in Lead II; prolonged Q-T in second record.

Discussion. It is illogical to presume that the steady increase in the proportion of abnormal electrocardiograms as more and more tracings were made annually (Section I) was primarily attributable to the more frequent resort to this diagnostic method; for although heart disease may now be called "captain of the men of death," it is certainly not yet an associate of the majority of the sick, and the relative occurrence of electrocardiographic abnormalities would show a decreasing increment as abnormal records are looked for more generally and with less discrimination. We believe, therefore, that these observations, together with the unexpected results of the samplings dealt with in Section II imply a more judicious and intelligent application of this laboratory aid coincidental with its increased employment, and from this one may, further, infer that a more liberal use of this diagnostic method does not necessarily result in wasteful expenditure of laboratory service. The additional discovery of a considerable number of electrocardiographic abnormalities in a significant proportion of patients who were regarded as free from cardiovascular disease (Section III) is direct evidence in support of a prevalent view that a full appraisal of the cardiac status is not complete without this adjunct to supplement the history, physical examination, functional tests, and roentgenographic study.

As to the significance of the unexpected abnormalities encountered, a valid general appraisal is admittedly difficult to make.

In the first place, the bases upon which we separated the expected from the unexpected abnormalities were necessarily arbitrary even though our approach was deliberately objective. Nevertheless, modification of the criteria of judgment in one direction or another does not enhance the results. Thus, if the clinical features that define an unexpected abnormality are made narrower and more rigid, the number of unexpectedly abnormal records naturally rises; while, if the clinical features defining an unexpected abnormality are made broader and more inclusive, the number of normal tracings increases unreasonably.

In the second place, some of our unexpectedly abnormal records might be explained, *a posteriori*, by a history like that of trichinosis some years before or diphtheria in childhood. If the validity of such explanations could be established, then some of the unexpected abnormalities we encountered may have no present or future clinical importance at all. However, in other patients the discovery of similar unexpected abnormalities may be highly significant. For example, T-wave abnormalities or heart block (A-V or I-V) in the diabetic patient or the subject with Buerger's disease may imply current coronary heart disease and progressive cardiac damage with definite prognostic inferences.

Thirdly, although a considerable portion of the electrocardiographic abnormalities was found among the older age groups, this might not be considered surprising, for coronary heart disease is common among them, the nature of such heart disease is partieu-

larly prone to produce electrocardiographic alterations, and changes in the tracings are more to be expected in any heart disease as it ages with advancing years. As a matter of fact, the occurrence of unexpected abnormalities was consistently lower in the older than in the younger age groups with the criteria we followed. Old age *per se* is not a cause of such abnormalities. It seems quite likely, therefore, that the unexpectedly abnormal electrocardiograms in the older patients indicate cardiac involvement not otherwise apparent.

Finally, the actual significance of certain familiar electrocardiographic abnormalities is not yet clearly established, for the category of abnormal features is built up largely from studies on patients with known or suspected heart disease instead of statistical analyses of large groups of normals. For example, low voltage occurred in 22 of the 400 patients examined in Section III of this study, and in 18 subjects this finding occurred in the absence of any presumptive evidence of heart disease. Wilson¹⁰ found low voltage in less than 1% of 100 normal subjects, which suggests that this feature was abnormal. However, Willis and Killins⁹ stated that in 68% of 140 cases showing low voltage there was no apparent heart disease, and unpublished studies³ made in this laboratory of 50 cases exhibiting low voltage included 15 patients in whom heart disease was not otherwise established. Thus, while low voltage may be an electrocardiographic abnormality, its significance and relation to heart disease is still uncertain in our opinion. Similar considerations may perhaps apply to other electrocardiographic abnormalities, such as unusually low, flat, or diphasic T waves.⁸ The serial changes in T noted by Chidsey² in patients with acute infectious diseases suggest at least transient myocardial involvement. Perhaps such changes mean no more than abnormal findings in the urine encountered transiently in conditions other than primary disease of the kidneys, but the facts indicate that the electrocardiogram, like the urine analysis, may furnish evidence of such involvement which may not otherwise be clinically apparent, and may influence views bearing on diagnosis, prognosis, and convalescence, the validity of which can be proved only by further experience.

If on the other hand, most of these abnormalities should prove meaningless, then our unexplained abnormal findings are but few and may cause no further concern. We are not prepared, therefore, to recommend electrocardiography as a routine examination, although it appears fully as capable of revealing obscure disorder as the more conventional routine blood count and urine analysis. Our results oblige us, however, to view electrocardiography as a desirable laboratory test not only in cardiac patients but also in those with diseases that are known or suspected to involve the heart secondarily, and in all elderly subjects. Our study indicates that wide general use of this laboratory method is amply justified by its

frequent disclosure of unexpected abnormalities which may prove to imply cardiac involvement that would otherwise escape detection.

Summary. Inquiry into the clinical helpfulness of a large and steadily increasing demand for electrocardiograms in the New Haven Hospital and Dispensary revealed that the proportion of abnormal records obtained has grown considerably and has practically paralleled the increasing demand, and that the clinical value of a representative group of records in a year of high demand was fully as great as in an earlier year when records were requested only half as frequently.

A study of the results of routine electrocardiography disclosed a significant incidence of electrocardiographic abnormalities beyond that which might be expected from other clinical evidence.

Conclusion. The increasing use of electrocardiography in local hospital practice appears justified. Requests for routine unnecessary electrocardiograms are decried, but their liberal use, if applied judiciously and intelligently, discloses abnormalities of clinical value sufficient to warrant the extra expenditure of laboratory service.

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THE DANGER OF PROCRASTINATION IN BILIARY TRACT DISEASE UNTIL IRREVERSIBLE LIVER AND KIDNEY CHANGES OCCUR.

BY ABRAHAM O. WILENSKY, M.D.,
NEW YORK, N. Y.

THE terminal phase of biliary tract and liver disease is the result of the progression of certain events, the pattern of which appears to be uniform. The pattern has been labeled "cholemia" misleadingly, for the picture is not entirely dependent upon the presence of icterus or hyperbiliruria. A much better term would be "hepatic insufficiency." Most of the cases presented, in addition, evidences of severe renal (hepatorenal syndrome) damage. While the picture is outwardly more or less uniform, many inconstant, interesting and unexpected functional and pathologic phenomena have occurred in other organs, showing that the results of hepatic insufficiency are far-flung.^{6a-c}

The exact factor in hepatic insufficiency which is responsible for the various organ changes is at the present writing unknown. The observation that necrosis of liver cells was associated with changes in the renal parenchyma and consequent renal insufficiency led some men to postulate the liberation of a nephrotoxic poison from the necrosed liver cells. Helwig and Schultz⁴ in cases of liver pulpification, and Fitz-Hugh² in cases of common duct obstruction with infection believed the mechanism to be definitely nephrotoxic, and incriminated infection as the chief cause. The association of liver damage and renal insufficiency has been reported too often to be merely a coincidental finding. However, there is little experimental proof for this relationship. The association may be merely the result of a disturbed water balance and Mann's⁵ work on hepatectomized animals would tend to corroborate this. Edema occurs in hepatic insufficiency, but this may be the result of cardiac failure or of a disturbed relationship of blood proteins which occurs in liver disturbances. It is even conceivable that the hepatorenal syndrome may be the result of an absence or diminution of some factor, possibly hormonal, which is elaborated by the liver. Bile retention does not cause the profound changes, since jaundice is not necessarily a part of the picture. Though biliary nephrosis is not uncommon in obstructive jaundice, these patients may go for long periods of time without developing hepatonephritic toxemia. Circulatory vasoconstriction or vasodilatation has been adduced as a possible cause of these interrelated hepatorenal changes because of their intimate embryologic blood supply.

The clinical picture of biliary tract and hepatic disease terminating with oliguria, anuria and uremia is fairly well known. I have observed this quite frequently and feel that this is a common mode of exitus, but I do not believe that the effects are specific for the kidneys alone. In 10 cases which came to postmortem examination the hepatorenal syndrome was applicable to 6. In 3 cases the predominant terminal phase was cardiac and 1 case presented an unusual blood picture resembling a subleukemic myelogenous leukemia.

It has been my observation that in common duct obstruction the outcome is favorable, provided infection does not set in in the biliary tree. Once infection gains a foothold, whether the obstruction is relieved or not, the entire picture changes and the course is frequently rapidly downhill. Operative release of common duct obstructions is often too late subsequently to reverse the preceding sequence of events. The resulting cholangiohepatitis does not bear any relationship to any particular bacterial organism, although the latter is probably derived from the alimentary canal. The quantitative extent to which the liver parenchyma is functionally involved will determine the final outcome, but frequently there are no recognizable corresponding anatomic changes. Oertel, Stadelmann and Eppinger, Jr., have pointed out that some activity liberated in the

liver cell environment disturbs the normal cell function so that it is unable to neutralize the toxins which result from normal digestive processes or other sources. Infection in the biliary radicals is not the only means of causing sufficient liver damage to produce the terminal picture, for direct trauma with pulpification of the liver and other mechanisms have produced the liver-kidney syndrome.

In my cases the characteristic changes found in the kidneys were marked degenerative changes in the tubules, and at times in the glomeruli, with occasional hemorrhages in the renal parenchyma. One case presented miliary abscesses. Myocardial changes, when present, were also of a degenerative nature. The case presenting an unusual blood picture showed hyperplasia of the myeloid structures. All cases presented a severe degree of periportal cellular necrosis of the liver.

Case Reports. CASE 1.—For the preceding year a 52-year-old woman had complained of abdominal cramps, gastric eructations, epigastric pain radiating to the back and right shoulder, without jaundice or change in the color of the stool. The patient was not acutely ill, but was elderly in appearance and obese. The laboratory findings included: 1, Roentgen ray visualization of a single gall bladder stone; 2, icteric index of 11.2; 3, an indirect Van den Bergh of 0.7 unit; the other findings were of no particular importance.

The operative exploration showed: pericholecystitic adhesions, a chronic cholecystitis with one large stone and an old healed duodenal ulcer. For 3 days the patient seemed to do well, then fever developed; there were questionable signs in the left lung; there was rapid subsequent deterioration and exitus occurred on the following day.

The postmortem examination showed: periportal inflammation in the liver parenchyma with fatty infiltration in a cirrhotic environment and an acute parenchymatous nephritis.

This is the more or less typical case of chronic gall bladder disease with subacute cholangitic infection which terminates fatally within a few days after operation, the trauma of operation probably acting as an impetus for the infection to become more fulminating. Although the laboratory study was inadequate, the clinical course indicated that this case terminated with renal failure, since outside of the liver the chief histologic changes were found in the kidneys.

CASE 2.—A 65-year-old patient was admitted in a second abdominal episode with jaundice, daily chills and fever, and right upper quadrant pain of 6 days' duration, after a free interval of 5 years. The pain was not severe but the jaundice had deepened, the stools had become yellow and the urine very dark. A persistent hiccough was present.

The patient was an elderly, well-developed, rather obese, white male, markedly icteric, acutely ill, and in very bad general condition. The abdomen was slightly distended; and there was marked costal tenderness and percussion tenderness over the lower right ribs. The liver was enlarged to 3 cm. below the costal margin. No other masses or viscera were palpable. The rest of the examination was relatively negative.

Although operation appeared urgently indicated, the patient's general condition was too precarious for any form of surgery. There were toxemia, chills and high fever, a clay-colored stool, increasing abdominal distention,

oliguria, a non-protein nitrogen of 117 mg. per 100 cc. and an increase in the icteric index. The patient died.

The important laboratory data were the following: icteric index, 94.5 to 137.3; Van den Bergh, direct immediate and 17 units indirect; blood urea, 31.1 mg.; non-protein nitrogen, 117.6 mg.; creatinine, 2.73 mg.; urine, bile + + + +; blood culture, *B. subtilis*.

This case presented the severest type of liver-induced injury to the renal mechanism. The terminal picture included oliguria, anuria and uremia, and the azotemia was well marked quantitatively.

CASE 3.—A 60-year-old white female, comatose and in moribund condition, had had during the preceding year progressive anorexia, bronzing of the skin, and loss of weight. An acute episode of severe right upper quadrant pain had ushered in the present emergency. There were marked toxemia, emaciation, dehydration and jaundice. Many of the toxic manifestations were referable to the central nervous symptoms. The only objective findings were marked tenderness in the right upper quadrant and a slightly enlarged liver. Death occurred on the day following admission.

Laboratory data included: hemoglobin, 102%; red blood count, 5,200,000; white blood count, 23,500; neutrophils, 50%; urine, smoky, acid, no albumin, small number of casts; Wassermann and Kahn, negative. Blood chemical studies: sugar, 178.6; urea nitrogen, 21; non-protein nitrogen, 21; uric acid, 3.6; creatinine, 1.28; icteric index, 63.3; Van den Bergh direct immediate; indirect 5.1 units/100 cc. serum.

This case presented the picture of a long-standing progressive obstructive jaundice in which the hepatic insufficiency intervened suddenly, probably as the result of a sudden complete tightening of the obstruction, no doubt precipitated by an overwhelming infection. The ensuing toxemia was marked by symptoms referable to the central nervous system.

CASE 4.—Ten days before admission, a 58-year-old man, the subject of angina pectoris for the preceding 7 years, complained of epigastric pain which was followed by a gradually increasing, intense jaundice. Weakness and languor were marked at the onset and for the 2 days before admission, mental changes were evident: restlessness, delirium, and finally coma.

The physical examination revealed an elderly well-nourished, extremely restless, comatose, cyanotic individual, with stertorous breathing, and marked jaundice. Pupils were slightly irregular, dilated, fixed to light and slow nystagmus was present. There were exophthalmos and markedly icteric sclerae but the fundi were normal. The lungs were emphysematous. The cardiac sounds were distant, and a harsh systolic blowing, non-transmissible murmur was present at the apex. The area of liver dullness was distinctly diminished. No other masses or viscera were palpable. There was marked hyperreflexia, with bilateral ankle clonus and Babinski. The abdominal and cremasteric reflexes were absent. The rest of the physical findings were of no clinical importance.

There was definite oliguria with terminal anuria. The urine contained a large amount of albumin, an occasional red and white blood cell and many hyaline and granular casts. However, no leucine or tyrosine crystals were present; and there was no glycosuria or acidosis. Bile and urobilinogen were present in the proportion of 1:10.

The blood chemical studies were as follows: glucose, 61.7 mg.; non-protein nitrogen, 67.4 mg.; creatinine, 1.21 mg.; chlorides, 410 mg. per

100 cc. whole blood; CO_2 combining power, 30.5 vol. %; icteric index, 61.9; Van den Bergh—immediate direct, 5.3 units indirect. The Wassermann and Kahn tests were negative and no heavy metals or other poisons could be found in the gastric contents. The hemoglobin was 92%; the red cell count was 4,900,000; the white blood cells numbered 21,800 with 83% neutrophils.

The patient lived for 14 hours after admission to the hospital. There were terminal fever, restlessness, flaccidity and Cheyne-Stokes respiration. Death occurred in cardiac collapse.

This case presented the picture of a subacute yellow atrophy with severe renal impairment and with unusual cerebral symptoms. It is possible that the hyperglycemia may have contributed to the picture, but it is apparent that the cerebral symptoms are out of proportion to the degree of demonstrable anatomic change.

CASE 5.—A 40-year-old female, who had had 2 children, was admitted because of pain in the right upper quadrant radiating to the back. The last menstrual period 2 weeks before admission was unusual in that she bled for 10 days. Since the onset there were progressively increasing jaundice, clay-colored stools, pruritus, nausea, anorexia, weakness and a loss of 15 pounds in weight; and, although there had been no further attacks of abdominal pain, a sense of soreness persisted in the back.

The physical examination revealed a middle-aged, well-nourished, markedly jaundiced, white female, in whom there was practically no palpatory localizing signs.

On admission the patient complained of nausea and a feeling of weakness. On the seventh and eighth days she had a slight chill and a rise of temperature to 103°F . An unusual blood picture, namely, an aplasia of the blood elements then developed until the white cell count fell to 350 cells with marked relative lymphocytosis. A number of myeloblasts were found on careful search. The red blood cell count, hemoglobin content and the number of the platelets likewise kept falling. Transfusions were without avail. A myeloid leukemia was suspected but a sternal marrow puncture revealed nothing diagnostic. The icteric index, which had previously been rising steadily, began to fall with the onset of the fever. Urobilin appeared in the stools and urine. The cholesterol esters began to fall. Urine excretion was abundant even in the presence of an increasing azotemia. The phenolsulphonephthalein excretion was undeterminable. Toward the end, there were increasing weakness, dyspnea, elevated temperature, muscular twitchings, delirium and terminal coma; exitus finally occurred.

This case was unusual in that the hematologic picture showed a rapidly progressive aplasia of all the blood elements with the appearance of very immature myeloid cells, so that antemortem, the diagnosis of myelogenous leukemia was made. The histopathology did not bear this out, and again we have an illustration that liver damage may have widespread, protean and, at times, most unusual and bizarre effects.

CASE 6.—A 45-year-old, obese, white woman was admitted to the hospital because of frequent episodes of nausea, retching without vomiting, and intermittent attacks of severe hypochondriac pain. Finally, pruritus was present; the urine became dark and the stools clay-colored; marked jaundice developed. Nevertheless, the patient was relatively comfortable and did not appear acutely ill. There were several small hemorrhagic spots on the

abdomen. The heart and lungs were negative. There was marked tenderness with some rebound tenderness in the right upper quadrant, but without rigidity. No masses were palpable, but the liver was slightly enlarged.

The laboratory data included the following: Wassermann and Kahn tests, negative; hemoglobin, 110%; red blood count, 5,400,000; white blood count, 6700 with 70% neutrophils. Blood chemical studies: chlorides, 271.1 mg.; glucose, 99.5 mg.; urea nitrogen, 114.8 mg.; uric acid, 219 mg.; icteric index, 191.4; Van den Bergh, indirect, 18 units; bleeding time, 2 minutes; coagulation time, 5½ minutes; urine, yellow, acid, sp. gr. 1.016, 4+ bile, no urobilinogen, occasional leukocyte; stool, no bile salts present.

After preliminary, not completely satisfactory preparation, she was operated upon. A chronically diseased gall bladder was found, and stones were present in the gall bladder and in the common duct. The patient did well for 8 days. Then she became drowsy and the temperature rose to 102° F. A diffuse erythema multiforme-like rash appeared, with oliguria, drowsiness and terminal coma. Exitus occurred on the fourteenth day.

The postmortem examination demonstrated an obstructive jaundice due to stenosis of the common bile duct and stones; a toxic hepatitis; an acute nephritis; multiple abscesses of kidneys; and a localized plastic peritonitis. The liver showed marked destructive changes with attempts at a compensatory hypertrophy; diffuse fibrous rupture of the bile capillaries and hemorrhagic infiltration of parenchyma; dense fibrosis in areas with almost complete obliteration of the normal liver elements. The kidneys showed diffuse hemorrhagic and degenerative changes in the tubules and glomeruli.

This case presented an unrelievable common duct stenotic obstruction with hepatic insufficiency. A fatal termination was inevitable. Although the case is presented as an example of the liver-kidney syndrome, the general infection and the local suppurative foci in the kidneys and in the peritoneum must not be lightly dismissed, and were surely the final irreversible and dominant cause of death. This association occurs so often that its importance must be stressed.

CASE 7.—In a 58-year-old female with cardiac disease a cholecystectomy, done for chronic cholecystitis and cholelithiasis, was followed in the succeeding 5 years by increasingly frequent recurrent attacks of chills and fever, agonizing right hypochondriac pain with vomiting and jaundice, with clay-colored stools and highly colored urine.

The physical examination revealed a groaning, dyspneic, cyanotic, icteric person. The heart was not enlarged to percussion; the sounds were fair and the pulmonic sound was louder than the aortic. The cardiac rate was, however, totally irregular. The lungs were clear. The abdomen was obese, distended, rigid on the right side with tenderness in the right hypochondrium and epigastrium; and the liver was enlarged.

A severe chill with temperature of 105° F., cyanosis and semicoma intervened quickly and the patient died 9 hours after admission in cardiac failure. No laboratory work-up was possible.

The postmortem examination showed cholelithiasis, stenosis of the bile duct, acute and chronic suppurative cholangitis and hepatitis; toxic form of nephritis; splenomegaly and acute splenitis; chronic pancreatitis; diffuse fibrillary myocarditis and atheroma of the aorta.

This case presented a long-standing incomplete common duct obstruction with infection in the biliary radicals. Drainage through the common duct was at first sufficient to take care of the infection; but finally the drainage became incomplete and the infection then

overwhelmed the hepatic cells, producing liver insufficiency. Nevertheless, the immediate termination was a cardiac phenomenon, based upon an old endomyocardial lesion, and fatally exacerbated by the overwhelming infection.

Among cardiologists, the deleterious effect of a focus of infection upon cardiac lesions is so well known either as an inciting or contributory agent that a cardiac lesion has at times been the deciding factor in determining operation upon the biliary tract apparatus. Beneficial effects upon the cardiac condition have followed many of these operations. This should emphasize the advisability of early operative attention to gall bladder and liver conditions.

Evidence of severe renal damage was also present; this completes the clinical picture of the hepatorenal syndrome; and there is no doubt that, had the patient continued existence, the terminal phenomena would have been those of renal insufficiency.

CASE 8.—In a 48-year-old man there was a history of a long-continued dyspepsia and episodes of epigastric pain associated with vomiting, light-colored stools, jaundice and latterly with chills and high fever. The impression given by the present 7-day-old episode was that the jaundice was of an obstructive nature with a superimposed cholangitic infection.

Physical examination revealed an acutely ill, icteric, cyanotic, white male. The lungs were clear except for an occasional sibilant râle. The heart had a soft blowing systolic murmur at the apex. There was rigidity of the upper rectus muscle with exquisite tenderness in the epigastrium. The liver was slightly enlarged.

The laboratory studies showed the following: hemoglobin, 58%; red blood cells, 4,600,000; white blood cells, 10,900; neutrophils, 70%; blood sugar, 101.5 mg.; blood urea, 13.4 mg.; creatinine, 1.41 mg.; cholesterol, 109.9; esters, 59%; Van den Bergh, direct 28.1 units; phenolsulphonephthalein, 10% in 2 hours; stools negative for blood; clay-colored; stomach analysis: free acid 20, total 44, no bile; bleeding time, 2 minutes and coagulation time, 4 minutes; urine, bile present.

The original impression, *i. e.*, obstruction plus infection, was confirmed. There was continued oliguria despite a satisfactory intake, but there was no azotemia, even though there was only 10% excretion of phenolsulphonephthalein in 2 hours.

It was not possible to prepare the patient suitably for operation and the symptoms continued. On the seventh day after admission he developed substernal oppression, a choking feeling, a fear of impending death, weakness, a totally irregular heart rhythm, and electrocardiographic evidence of auricular fibrillation with frequent ventricular extrasystoles. The general condition rapidly became critical, and exitus followed shortly thereafter.

The postmortem findings were: jaundice, ascites, nutmeg liver, congested fibrotic spleen, chronic peritonitis, chronic pleuritis, healed apical tuberculosis, contracted edematous gall bladder, dilated common duct, subepicardial, subendocardial and intramural hemorrhages; lymphoid hyperplasia.

This case presents a long-standing gall bladder disease with the sudden intervention of obstructive jaundice and cholangitis. There undoubtedly was some renal impairment present but the immediate terminal picture was a cardiovascular collapse, suggestive of sudden coronary occlusion.

Discussion. This series of biologic events has its inception in the biliary environment and begins usually before the fortieth year of life. In the initial primary stage of this disease, the process, for practical purposes, is limited to the gall bladder. The important facts that clinical experience has demonstrated are that in this stage the disease occurs in younger subjects, the general health is good, there are no complicating factors anywhere else in the body, the results of surgery are excellent, and the mortality is very small. These facts are true when the disease is brought under control at a fairly early period of its development, when the patients are under forty years of age and when preliminary medical treatment has not been unnecessarily prolonged.

If unchecked, the further progression of the disease occurs slowly and frequently extends over a span of life up to 20 and more years. The consequences occur most commonly in the fifth and sixth decades of life. Infection enters the picture sooner or later; then the process spreads upwards through the biliary tract; and presently, various forms and degrees of obstructive jaundice follow with secondary effects in the kidney. If reversal of the process and especially of its dangerous component, jaundice, is not promptly accomplished, a whole series of potentially more dangerous consequences develop, characterized by destruction of the liver parenchyma, secondary degenerative destructive changes in the kidney and anatomic changes in other organs which are commonly irreversible forerunners of a rapid and fatal termination.

The renal changes are often more marked than those in the liver; they often dominate all the other manifestations; and the terminal picture is that of "uremic poisoning," so that the renal picture may be taken as a measure of the severity of the entire disease. Nevertheless, the apparent rapidity of the terminal stage cannot alone be accounted for by the renal damage. Pathologic changes occur and coexist in other important organs which destroy the ability of the individual to withstand the damage of the combination of primary liver and secondary kidney disease, with or without the traumatic insult of any necessary operation. In a generic way these include: changes in metabolism, notably obesity, degenerative changes in the myocardium and more or less acute closures in the coronary vascular circulation; profound disturbances in less acute closures in the coronary vascular circulation; profound disturbances in the hemopoietic system resembling a blood dyscrasia; and resultant toxic disintegrating manifestations in the central nervous system.

Obesity. In the above series of cases, 70% of the women and 37% of the men were definitely obese. The association holds special relationship and importance to women, possibly because of the child-bearing function and consequent metabolic disturbances in

the lipoid (cholesterol) substances. In any case, practical clinical experience teaches the marked decrease in capability of resistance to infection, and to any form of operative insult.

Glycosuria. Glycosuria is an important complication of gall bladder disease in patients above 40 years of age. It is important to distinguish the group with associated pancreatic disease and the group with the ordinary forms of diabetes. With modern methods of treatment, glycosuria does not appear any more an important factor in the outcome of surgery for gall bladder disease.

Cardiac Disease. In preoperative electrocardiographic studies evidences of old coronary artery closures and of myocardial infarction are rather common. The latter should not be a necessary deterrent to surgical intervention, as with good care, the proper form of anesthesia and a rapidly performed operation, the great majority of the patients do well.

Cardiovascular collapse on a myocardial basis is a frequent terminal event. This usually occurs in those cases in which gall bladder disease and mild cholangitis have been present for a long time. The cardiac symptoms we have observed have been disturbances of rhythm with central and peripheral collapse.

Cardiac disease of this type is, generally speaking, a coincidental development during the years of elaboration of the entire gall bladder-liver-kidney sequence. And although, possibly, at the beginning, the heart lesion and the biliary tract lesion are independently derived, it is a clinical fact that sooner or later the two become interrelated. Universal experience has taught the lesson that any form of surgery, and especially biliary tract surgery, had better be practised before this complication appears, because cardiac disease contributes to and increases the mortality of operation to a large extent.

Acute coronary artery closures are much less commonly seen after operation upon these patients. They carry even a greater risk than under ordinary conditions.

The possibility of adequate preparation of the cardiac factor so that patients can overcome the added trauma of operation is undoubtedly related to the reserve powers of the individual heart. At the present writing this reserve cannot be estimated at all accurately for clinical purposes. Then the question of operative interference is a very difficult one to decide, frequently because of the impossibility of judging the operative risk. Nevertheless, operative intervention is imperative when any jaundice is present.

Hematologic Complications. The association of chronic liver disease, cirrhosis of the liver, and the blood picture of a macrocytic anemia is quite well established. In chronic disease of the liver there results a failure of storage of the factor necessary for the maturation of the red cells. Greene³ has pointed out that this fac-

tor is present in acute yellow atrophy. None of our cases presented the blood picture of a macrocytic anemia, but hypochromic anemias were quite common. The unusual blood picture of Case 5 was probably not the result of an absence of some hemopoietic element from the liver, but rather the result of hepatic toxemia. I have had other similar experiences. I have observed, also, that many cases of hepatic insufficiency presented leukopenia, and 1 case presented thrombopenia. Hence depression in, or destruction of, the formed elements of the blood stream is probably another manifestation of hepatic insufficiency.

Symptoms Referable to the Central Nervous System. There is no pathologic evidence of any cerebral changes; but the presence of marked cerebral symptoms cannot always be explained on the basis of renal failure or the presence of any other abnormality which is commonly associated with them.

Relation to the Hepatorenal Syndrome. The association of hepatic and renal disease following primary gall bladder disease is only one of the many mechanisms of the much discussed "hepatorenal syndrome." In clinical medical and surgical practice there is widespread distribution of hepatorenal symptoms with or without lesions. One cannot escape the conclusion that the association of hepatic and renal pathologic conditions is necessarily frequent, because of the extraordinary biologic and functional intimacy of both of these extremely important organs. It seems that the two essential anatomic factors in this association do not occur in every case in the same intensity and proportion. Once this train of functional and anatomic disturbances begins, however, other factors come into play, such as fever, shock, autolysis of tissue, anoxemia, anhydremia, and azotemia, and the primary injury is enormously accentuated. The difference in the symptoms, in the suddenness and dramatic effect of the terminal clinical manifestations and in the rapid culmination in death seem to have most important relations to these various diverse, yet interlocking factors.

Conclusions. The great danger of withholding adequate treatment in this group of cases until irreversible changes occur is well shown by these individual clinical experiences. The lesson must be thoroughly learned that energetic treatment is necessary as soon after the inception of this pathologic process as is possible, when the lesion is limited to the gall bladder and biliary tract environment in order to obviate any possibility of the occurrence of any of the severe and dangerous manifestations which occur in the further biologic development of this disease and in order to eliminate the extra hazard which the presence of important cardiac and other associated lesions carry. The most important objects to be accomplished by surgery are: 1, the thorough removal of any focus of infection; and 2, the thorough removal of any obstruction to the unhindered outflow of bile into the intestine.

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AGNOGENIC CONGENITAL CLUBBING OF THE FINGERS AND TOES.

BY H. B. THOMAS, M.D.,

CHIEF OF METABOLIC CLINIC, YORK HOSPITAL, YORK, PA.

CLUBBING of the fingers and toes has been recognized since the time of Hippocrates as a manifestation of certain forms of intrathoracic disease. In 1889 von Bamberger¹ described the general thickening and sclerosis of the long bones which is frequently associated with clubbing. The following year Marie² unaware of Bamberger's work gave a full description of this syndrome and suggested the name "secondary hypertrophic pulmonary osteoarthropathy." Since that time there have been numerous studies and case reports most notably those of Locke⁷ in 1915 and 1920 in which the literature was reviewed and brought up to date. There has been little information added up to the present time, except the term "acropachy" (thick extremity) has been suggested to designate the clubbing of the fingers and toes.

Hypertrophic osteoarthropathy may be defined as a disease, usually secondary, occurring in the course of various chronic conditions, characterized by a general and symmetrical hypertrophy of the distal phalanges with resulting clubbing (acropachy), frequently accompanied by enlargement of some of the other bones in the hands and feet or by hypertrophy of the bones of the forearm and legs, and in the late stages, by involvement of the joints. Clubbing may be present without any bone changes and in some cases well marked osteoarthropathy occurs without the characteristic clubbing. These variations have aroused a great deal of controversy whether or not these two conditions were related or independent but the evidence seems to favor the opinion that the two conditions are identical and part of the same disease process.

Three clinical types of the disease have been described by Sternberg:¹¹ 1, clubbing of the fingers and toes without changes in the long bones; 2, a combination of clubbing and painful thickening of the long bones, especially in the forearms and legs as described by von Bamberger; and, 3, an advanced stage in which there is conspicuous general and painful deformity and the primary disease is overshadowed by the severity of the osteoarthropathy originally described by Marie.

It is well recognized that the changes in the digits and skeleton are nearly always secondary to some primary disease in the lungs, heart, liver or some other part of the body, suppurative pulmonary disease being most frequently the cause. This secondary form of the disease is well recognized but the mechanism of production of the changes is not known as yet. In certain rare instances clubbing of the digits with or without bone changes occurs in individuals in whom no apparent cause can be found by any clinical or laboratory methods. Some of these cases are familial and some congenital.



FIG. 1.—Hand showing marked clubbing.

Witherspoon¹⁴ in 1936 reviewed the literature on congenital and familial clubbing, finding reports of 14 instances in addition to his case. In the congenital or familial type there is rarely progression from clubbing alone to the hypertrophic osteo-arthropathic type. This latter type is quite uncommon as Locke was able to collect only 5 instances from the literature in 1915; since that time H. M. Thomas, Jr.¹⁵ has added one following a thyroidectomy, and Hollar and Agnor⁵ have reported another in a negro male, aged 21. The case reported here is of interest because it portrays an instance in which there is clubbing of the digits of unknown cause associated with mild periosteal hypertrophy and occasional arthritic pain. This feature makes classification difficult; it probably represents mild or slowly progressive congenital chronic osteo-arthropathy.

Case Report. G. E., colored male, aged 22, was admitted to the York Hospital November 19, 1940, and discharged November 27, 1940. This

patient's condition was discovered in a routine health examination for the selective service. He has had clubbed fingers and toes as long as he can remember and has always enjoyed good health. He has never had any serious illnesses or operations except a tonsillectomy in 1926 from which he had an uneventful recovery. In 1935 he was given a routine tuberculin test to which he reacted. A Roentgen ray of the chest was taken at that time which revealed no lesion. He states that his father has the same condition but knows definitely that his brother does not; unfortunately, the father resides in another state and cannot be reached. The patient is a rather intelligent negro and I believe his observations may be correct. There are no other siblings. Family history is otherwise irrelevant. His subsequent history is completely normal except occasional pain in each

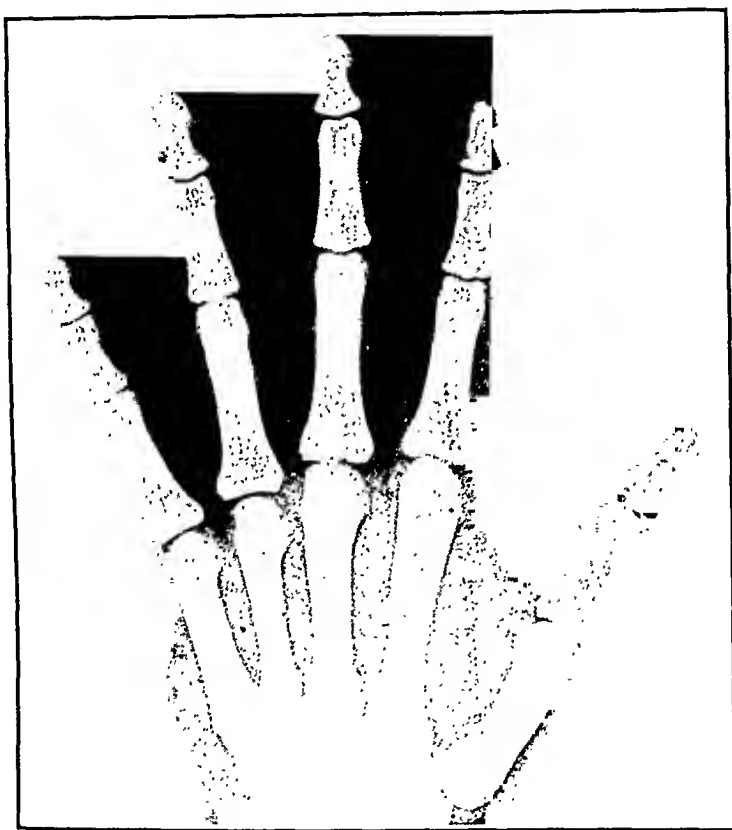


FIG. 2.—Clubbed fingers showing absence of spatulation.

knee after a period of excessive exertion. During his stay in the hospital his temperature, pulse and respiratory rates were normal. Other than the marked clubbing of all the fingers and toes the physical examination was not remarkable. There was a bulbous enlargement of the finger tips and toe tips, double curvature of the nails, and a considerable degree of cyanosis of the nail bed.

Urine examinations were normal. Hematologic studies were normal with the exception of a mild degree of anemia, the Hb. being 13 gm. and the R.B.C. 4.1 million. The blood Kahn test was negative. Electrocardiographic tracings were normal. The procholone time was 14 sec., the ether time 6 sec., and the venous pressure was 15 cm. of water.

Roentgen studies of the sinuses and chest were not remarkable. Lipiodol injection into the tracheobronchial tree revealed no abnormalities; the long bones were normal except mild periosteal thickening of each tibia.

Etiology. The theories concerning the production of secondary clubbing are numerous and exceedingly diverse, ranging from capillary hyperemia, defective oxygenation, circulating toxins, certain nervous diseases, syphilis, tuberculosis, avitaminosis to amyloid degeneration. No one mechanism is able to explain the changes without serious objection. It is not hard to understand

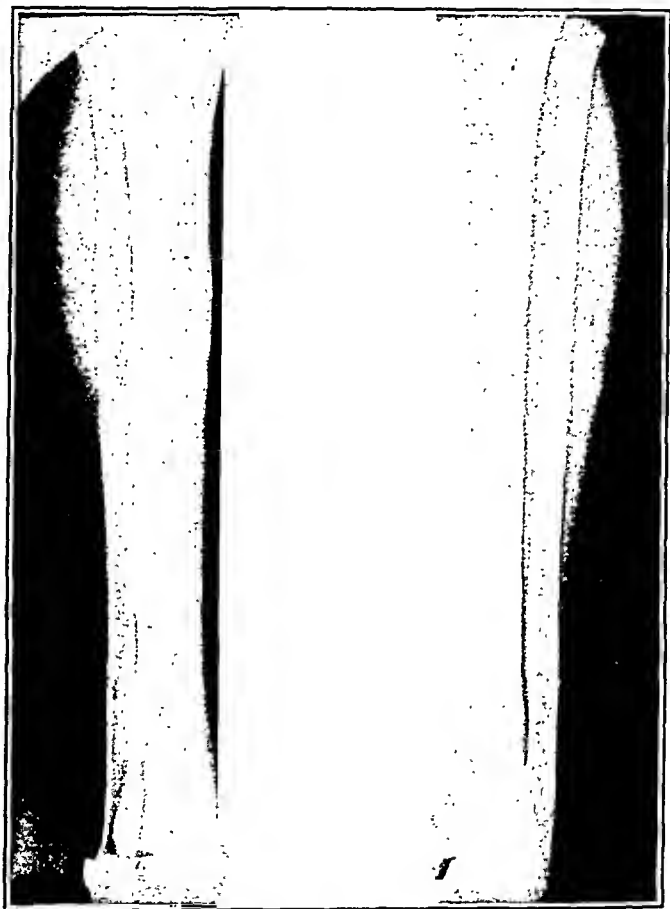


FIG. 3.—Bones of the leg showing a mild degree of periosteal hypertrophy.

that the method of production of primary or congenital clubbing is even more indefinite and hazy than the secondary form. At the present time there is no adequate explanation for the production of either form.

The gross appearance of clubbing is easily recognized and needs no further description. However, there has been no general agreement of the microscopie findings in the few cases studied. Campbell² states that there is an edematous condition of the tissues lying

between the nail bed and the bone. Freytag⁴ reported dilatation of the capillary loops in the bed with engorgement of the inter-papillary processes, but found no alteration in the skin, nerve changes or endarteritis obliterans. Therese¹² noted hypertrophy of the horny layer, papillæ and the connective tissue of the derma. Buzzard² noted an excess of subcutaneous fat, Schirmer¹⁰ found a tissue resembling embryonic mucoid and Thomas¹³ reported marked dilatation of the venous and marked tortuosity of the arterial capillaries of the nail bed.

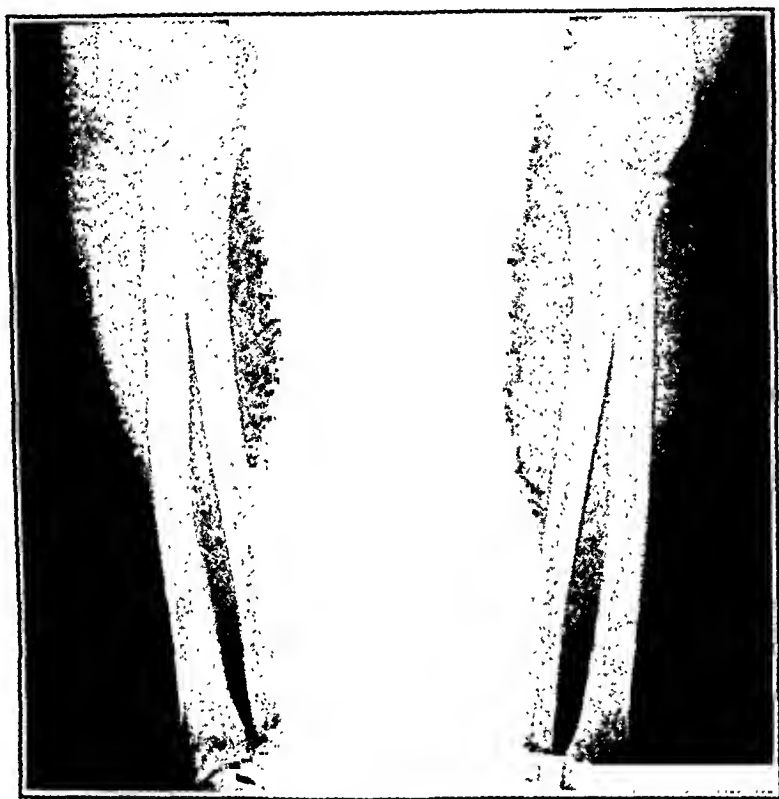


FIG. 4.—Bones of the forearm showing a very slight periosteal hypertrophy.

As the change in simple clubbing of the digits is usually confined to the soft parts there are no changes in a Roentgen examination of the digits in most cases. In a few cases there has been definite proliferation of the bone in the distal phalanges and Ragins and Freilich⁹ Kayne,⁶ and Witherspoon¹⁴ have reported a definite splaying of the distal phalanges in the familial type of clubbing. When there are changes of the long bones the hypertrophy of the bones in the terminal digits is more common.

Summary. 1. A case is reported of clubbing of the digits of unknown etiology—probably congenital and familial.

2. This instance represents a border-line situation between acropachy and chronic osteo-arthropathy.

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THE STANDARDIZATION OF THE CONGO RED TEST FOR AMYLOIDOSIS.

BY ALBERT TARAN, B.A.,

CHEMIST, SEA VIEW HOSPITAL,

AND

ALBERT ECKSTEIN, M.D.,

RESIDENT PHYSICIAN, SEA VIEW HOSPITAL,

STATEN ISLAND, N. Y.

(From the Department of Pathology, Sea View Hospital, Dr. Oscar Auerbach, Director.)

THE Congo red test has been used very extensively during the past few years to determine the presence of amyloidosis, especially in those patients who have been suffering from chronic pulmonary tuberculosis. At this hospital 22% of the cases which have come to autopsy revealed amyloidosis.

The test in the great majority of cases has proved very useful as a diagnostic procedure, although in many instances we have found it to be inadequate. The discrepancies occurred in those cases where the blood serum removed 4 minutes after the intravenous injection of Congo red was either too light or too dark in color, thus rendering the specimen inadequate for use as a standard for colorimetric comparison with the blood serum removed one hour after injection.

An attempt was made to investigate the reasons for such discrepancies and to arrive at a standard and uniform test.

It was found that in all cases where the greatest variations in color intensity occurred the body weights of the patients were either much greater or much less than 100 pounds. The 4-minute specimens were too light in color when the body weights ranged between 140 and 190 pounds. Conversely, when the body weights ranged between 40 and 70 pounds, the 4-minute specimens showed a strong color intensity.

The obvious factor involved then seemed to be the relationship between the amount of dye used and the body weight. In most institutions 10 cc. of a 1% solution of the dye are given to all patients regardless of body weight (according to Bennhold).¹

Keith, Rowntree and Geraghty,³ in determining blood volume with vital red, injected 1 cc. of a 1% solution of the dye per 5 kilos of body weight.

Osgood and Haskins,⁶ in giving the method for the Congo red test for amyloidosis, quote the procedure of Keith, Rowntree and Geraghty as modified by Harris,² for the estimation of blood volume. They state that one-fourth the body weight in kilos of a 1.5% solution of Congo red should be injected. This appears to be the first attempt at a standardization of the test for amyloidosis, since it takes into consideration both the blood volume and the body weight.

We have found at this hospital that the injection of 1 cc. of a 1% aqueous solution of the dye per 10 pounds of body weight gave standard specimens which closely approximated each other in color intensity and which could be used for colorimetric determinations. Any greater amount of dye, when used expressly as a test for the presence of amyloidosis, seems superfluous.

The standardized test given here includes a modification of the original Bennhold technique in the treatment of the blood prior to colorimetric comparison. This is the acetone extraction procedure devised by one of us⁸ to eliminate any hemoglobin which might be present due to hemolysis.

Method. Inject 1 cc. of a 1% aqueous solution of Congo red per 10 pounds of body weight intravenously. At the end of exactly 4 minutes, and then 1 hour, after the injection, obtain blood specimens of 10 cc. each and place them into clean, dry test tubes. Allow the bloods to clot and retract and then centrifuge them at a moderate speed for 10 minutes. Aspirate off the clear sera and place them into graduated centrifuge tubes. Add acetone equal to the volume of serum in each tube and shake them well. Centrifuge the tubes for 10 minutes at a moderate speed. Pour off the supernatant fluids and place them into micro cups of a colorimeter to be compared. Set the 4-minute specimen at 20 mm. and read the 1-hour specimen.

Calculation:

$$100 - \left[\frac{\text{4-minute specimen reading}}{\text{1-hour specimen reading}} \times 100 \right] = \text{per cent absorption}$$

For example: The 4-minute specimen is set at 20 mm. in the colorimeter. The 1-hour specimen reads 25. Therefore the per cent absorption of the dye is 20.

To prove the advantage of the standard test over the usual technique of using 10 cc. of dye for all patients, we performed a series of tests using known amyloid and non-amyloid cases. In one series of the non-amyloid group we performed tests with patients whose body weights varied greatly, each receiving 10 cc. of dye. As shown in Table 1 the 4-minute specimens varied markedly, the

difference between them ranging from 15 to 75%. In some instances, the 4-minute specimens were practically devoid of dye, making comparisons with the 1-hour specimens impossible. These cases typify the results obtained in a large hospital where many Congo red tests are performed and where 10 cc. of dye are injected into all patients.

TABLE 1.—NON-AMYLOID GROUP (50-175 POUNDS)—10 CC. DYE.

Case.	Body weight (pounds).	% dye absorption in 1 hr., using 4-min. specimen as standard.*	Suitability of 4-min. specimen as standard.	Comparisons between 4-min. specimens of different Congo red tests chosen at random.	
				Cases.	% variation.
1	76	55	Too dark	1 rs. 2	= 15
2	51.5	20	Too dark	1 rs. 3	= 45
3	153	50	Too light	2 rs. 5	= 60
4	170	No comparison possible	Too light	5 rs. 6	= 70
5	140	55	Too light	5 rs. 7	= 75
6	59.5	25	Too dark	2 rs. 3	= 68
7	63.8	30	Too dark	8 rs. 10	= 40
8	80	40	Too dark	1 rs. 10	= 65
9	167.8	No comparison possible	Too light	2 rs. 10	= 60
10	147	60	Too light	7 rs. 10	= 55
11	64.5	25	Too dark	11 rs. 14	= 60
12	51.8	20	Too dark	11 rs. 12	= 20
13	102	No comparison possible	Too light	12 rs. 14	= 55
14	142.5	60	Too light	10 rs. 11	= 65
15	171	No comparison possible	Too light	8 rs. 14	= 45
16	59	15	Too dark	16 rs. 17	= 72
17	142	60	Too light	16 rs. 19	= 10
18	163	No comparison possible	Too light	17 rs. 19	= 58
19	51	20	Too dark	17 rs. 20	= 60
20	60	25	Too dark	19 rs. 20	= 20
21	152	70	Too light	20 rs. 21	= 55
22	56	30	Too dark	21 rs. 22	= 60
23	70.5	35	Too dark	21 rs. 23	= 55
24	147.5	65	Too light	23 rs. 24	= 70
25	155.5	60	Too light	24 rs. 25	= 22

* 4-min. specimen represents zero absorption

Another group of non-amyloid patients was chosen with nearly the same body weights. Each of these patients received 10 cc. of dye. In this group all 4-minute specimens were satisfactory as standards and no marked deviations in them were found. The 4-minute specimens varied between 2 and 12%. The results of these tests can be seen in Table 2.

Not only did 4-minute specimens of patients whose body weights were in the vicinity of 100 pounds check closely, but also those of patients of greatly varying body weights, when they were given 1 cc. of dye per 10 pounds of body weight.

A group of amyloid patients was given injections of the dye according to the standard method outlined above. The criteria for the presence of amyloidosis in this group consisted of previous Congo red tests, which gave results ranging from 90 to 100% absorption, and clinical manifestations. These latter included enlarged, palpable livers and spleens and varying degrees of albumin-

uria. In previous works Lipstein and Auerbach⁵ and Lipstein⁴ have demonstrated the close correlation between the Congo red tests and clinical and postmortem findings. With few exceptions, amyloidosis was found to be present in greater or lesser degree in all cases having dye absorptions between 90 and 100%.

TABLE 2.—NON-AMYLOID GROUP (95-105 POUNDS)—10 Cc. DYE.

Case.	Body weight (pounds).	% dye absorption in 1 hr., using 4-min. specimen as standard.*	Suitability of 4-min. specimen as standard.	Comparisons between 4-min. specimens of different Congo red tests chosen at random.	
				Cases.	% variation.
1	101	60	4+	1 vs. 2	= 8
2	95.5	75	4+	2 vs. 3	= 10
3	104.8	50	3+	3 vs. 4	= 8
4	99.5	40	4+	4 vs. 5	= 12
5	102	45	3+	1 vs. 5	= 5
6	102.8	30	4+	5 vs. 6	= 2
7	104.5	40	3+	6 vs. 7	= 6
8	98.5	50	4+	7 vs. 8	= 9
9	100.8	35	4+	8 vs. 9	= 3
10	95.5	55	4+	8 vs. 10	= 2
11	98	25	4+	10 vs. 11	= 8
12	96.8	35	4+	11 vs. 12	= 3
13	101.5	45	4+	12 vs. 13	= 5
14	103	50	3+	13 vs. 14	= 10
15	99.8	45	4+	14 vs. 15	= 10
16	98.3	35	4+	15 vs. 16	= 10
17	101.3	30	4+	15 vs. 17	= 6
18	104	35	4+	16 vs. 18	= 5
19	101.5	45	4+	17 vs. 19	= 5
20	102.3	55	4+	19 vs. 20	= 8
21	97.3	50	4+	20 vs. 21	= 10
22	100.3	40	4+	21 vs. 22	= 12
23	101.5	35	4+	22 vs. 23	= 10
24	104.3	45	3+	23 vs. 24	= 10
25	102.3	55	4+	24 vs. 25	= 8

4+ = very good 4-min. specimen; 3+ = good 4-min. specimen.

* 4-min. specimen represents zero absorption.

In this group, which consisted of 42 cases, we again obtained values ranging from 90 to 100% absorption. The absorption in the majority of cases was 100%. No case was considered as 100% absorption unless the 4-minute specimen showed a good color intensity comparable to that obtained in the non-amyloid group.

The 4-minute specimens were satisfactory as standards with the exception of 11 cases. In each of these cases the 4-minute specimen was too light in color to be relied upon as a standard even though the dye was given in proportion to body weight. This led us to investigate the 11 cases further in order to obtain a standard test which would be as free from error as possible in the diagnosis of amyloidosis.

After a period of several months Congo red tests were repeated on the 11 cases in addition to most of the other amyloid cases (24) and on 60 additional non-amyloid cases. We adopted the procedure of obtaining three blood specimens, namely, 2 minutes, 4 minutes and

then 1 hour, after the injection of the dye, which was again given according to body weight. The reason for taking the additional blood specimen (2-minute) was based on our assumption that in the presence of widespread amyloidosis practically all of the dye was absorbed in less than 4 minutes.

The results of these experiments attributed to the adoption of our final standard test. In all 11 cases, as well as in the other amyloid cases, the 4-minute specimens were duplicates of what we had obtained previously. The 2-minute specimens, however, showed excellent color intensities. This gave us the desired information concerning the validity of the test as a diagnostic aid. Whereas previously these tests were reported as containing an insufficient amount of dye, they were now reported as 90 to 100% absorption with the assurance that a proper amount of dye was introduced into the vein. The differences between the 2-minute and the 4-minute specimens were marked. In some cases differences of as much as 75% were noted. Table 3 serves to illustrate this point.

TABLE 3.—AMYLOID GROUP—USING STANDARD TEST.

Case.	% dye absorption in 1 hr., using 2-min. specimen as standard.*	Comparisons between 2- min. and 4-min. specimens on each patient (% variation).
1	100	40
2	100	25
3	100	70
4	100	20
5	100	25
6	100	55
7	90	75
8	100	70
9	95	60
10	100	40
11	100	25
12	100	35
13	100	45
14	100	50
15	100	45
16	100	20
17	100	70
18	100	75
19	100	55
20	100	25
21	100	50
22	100	50
23	100	45
24	95	45
25	100	40
26	100	45
27	100	65
28	100	55
29	100	45
30	100	50
31	100	60
32	100	50
33	100	45
34	95	55
35	100	65

* 2-min. specimen represents zero absorption.

The differences between the 2-minute and 4-minute specimens in the 60 non-amyloid cases were not great. Table 4 shows that the greatest single difference in this group was 15%, with a mean deviation of 8%. The per cent of dye absorption of these cases was still within normal limits, that is, less than 90%.

The validity of this entire study is borne out by the fact that 21 of the 42 "amyloid" cases have since come to autopsy and each revealed amyloidosis of greater or lesser degree. Also, of the total number of non-amyloid cases under study (110), 20 cases have come to autopsy and only one revealed a moderate degree of amyloidosis. The Congo red test on this case was performed $4\frac{1}{2}$ months prior to death and yielded an absorption of 65%. It is entirely probable that amyloidosis had developed during this interim.

We concluded that the 4-minute specimen was inadequate as a standard where widespread amyloidosis was present. In its place we introduced the 2-minute specimen to serve as a standard for colorimetric comparison. In the case of complete absorption of the dye in the 1-hour period the 2-minute specimen serves as a standard, not from the point of view of comparison with the 1-hour specimen (which is devoid of dye), but to demonstrate to the clinician that a sufficient amount of dye was originally introduced into the vein. Since there were only slight differences between the 2-minute and the 4-minute specimens in normal subjects it does not matter materially that the 2-minute specimen is made a standard for colorimetric comparison.

Since the standard test described necessitates a larger amount of dye than most frequently used, it may be of interest here to mention a word about the toxicity of the dye. Richardson and Dillon⁷ have recently studied the toxic effects of intravenous injections of Congo red in animals and have found a high tolerance for the dye by cats, rabbits, pigeons and rats. They state that "the highest tolerated single doses in mgs. per kilo body weight were as follows; pigeons, 100; rats, 140; rabbits, 200; cats, 100." This demonstrates the wide margin of safety in using the dye intravenously.

Summary and Conclusions. 1. A standardized method for the Congo red test for amyloidosis is presented.

2. The dye is administered according to body weight. It was found that 1 cc. of a 1% aqueous solution of the dye per 10 pounds of body weight yielded more accurate tests than the fixed amount customarily used.

3. Tests were performed on amyloid and non-amyloid patients, using both the usual technique of injecting 10 cc. of dye regardless of body weight and the standardized method.

4. In one non-amyloid group patients were selected whose body weights were nearly the same (range between 95 and 105 pounds) and in the other those whose body weights varied considerably (range between 50 and 175 pounds). The former group showed consistently reliable 4-minute specimens, while the latter gave

TABLE 4.—NON-AMYLOID GROUP—USING STANDARD TEST.

Case.	% dye absorption in 1 hr., using 2-min. specimen as standard.*	Comparisons between 2- min. and 4-min. specimens on each patient (% variation).
1	30	5
2	35	5
3	25	8
4	40	10
5	65	8
6	50	6
7	55	8
8	40	5
9	45	15
10	40	5
11	65	10
12	70	6
13	75	5
14	30	5
15	35	8
16	20	7
17	35	10
18	45	10
19	45	5
20	40	6
21	65	5
22	60	5
23	50	8
24	55	5
25	45	10
26	30	10
27	25	10
28	35	5
29	60	10
30	30	8
31	35	10
32	50	5
33	55	5
34	60	10
35	65	12
36	65	15
37	60	5
38	55	10
39	50	10
40	55	8
41	40	10
42	35	8
43	25	5
44	20	5
45	25	10
46	60	8
47	65	5
48	60	8
49	60	10
50	50	10
51	55	8
52	50	5
53	55	8
54	65	9
55	60	10
56	55	8
57	65	8
58	70	10
59	75	12
60	65	8

* 2-min. specimen represents zero absorption.

4-minute specimens which differed by as much as 75%. In some cases the per cent absorption could not be computed because of insufficient dye in the 4-minute specimens.

5. In the amyloid group 90 to 100% absorption was a consistent finding. This is in so close correlation with previous work that such results must be obtained to indicate amyloidosis. In all but 11 cases the 4-minute specimens contained sufficient dye to be considered as appropriate standards.

6. These 11 cases were investigated further along with 24 of the other amyloid cases and it was found expedient to draw a 2-minute specimen in addition to the 4-minute and 1-hour specimens. A group of 60 non-amyloid cases was chosen as controls. In all of the amyloid cases, the 2-minute specimens showed good color intensity and the differences in color between them and the 4-minute specimens were marked (as high as 75%). There were only slight differences in color intensity between the 2-minute and 4-minute specimens in the non-amyloid group, the highest per cent variation being 15.

7. The 2-minute specimen was adopted as the colorimetric standard in place of the 4-minute specimen.

8. Since the inception of this study 21 of the 42 amyloid patients have come to autopsy and each revealed amyloidosis of greater or lesser degree. Twenty of the non-amyloid patients have come to autopsy and only one case revealed a moderate degree of amyloidosis.

9. The standardized method has improved the accuracy and reliability of the test as a diagnostic aid.

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THE EFFECT OF DIET AND MEALS ON THE MAXIMUM UREA CLEARANCE.*

BY L. P. LONGLEY, M.D.,

TEACHING FELLOW, WESTERN RESERVE UNIVERSITY MEDICAL SCHOOL,

AND

MAX MILLER, M.D.,

INSTRUCTOR IN MEDICINE, WESTERN RESERVE UNIVERSITY MEDICAL SCHOOL,
CLEVELAND, OHIO.

(From the Department of Medicine, Western Reserve University and Lakeside Hospital.)

AMONG tests of kidney function the urea clearance of Möller, McIntosh and Van Slyke¹ holds a deservedly popular place. Its

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precision in borderline cases, however, is impaired by a number of factors, aside from the state of the kidneys, which have been reported to effect its values. The influence of two of these, the previous diet, and meals, are the subject of this study.

In dogs, Shannon, Jolliffe, and Smith¹⁶ found the fasting urea clearance on a meat diet to be as much as double that on a cracker diet. Pitts¹³ found that a low protein meal had little effect, while meat produced a gradual and prolonged rise in clearances, whether the dogs had been on a basal or meat diet. Glycine, glycylglycine, and alanine had an effect similar to meat. Since the clearances were also increased by injection of thyroxin or phloridzin, Pitts concluded that protein metabolism as such, whether endogenous or exogenous, is responsible for the increase in renal function. Because the urea/xylose clearance ratio remained quite constant, the effect is better explained by an increased renal blood flow rather than by any change in the mechanism of urea excretion. Van Slyke, Rhoads, Heller, and Alving¹⁹ reached the same conclusion, and noted that administration of urea gave no change in the clearance.

In normal man,^{3,7} the changes are not so great as in the dog, clearances on low protein diets being usually about 30% less than those on more liberal protein intakes. But the change in clearance does not seem to be proportional to the protein intake, for the reduction was no greater on a 9- than on a 40-gm. protein diet, and ingestion of 280 gm. daily did not raise it above the level found on a 100-gm. diet.

Because of the probable effect of meals, it is usually customary to determine the urea clearance in the fasting state. However, MacKay⁹ showed that an ordinary breakfast had no effect on the standard clearance. If the same holds true for maximum clearance it would simplify the technique of the test.

The present experiments aimed to determine whether the urea clearance was proportional to the protein intake, or whether there was a critical intake at which it increased, and whether this corresponded with any change in basal metabolic rate or cardiac output. In addition, observations have been made of the effect of large and small meals on maximum clearance with both low and high protein diets.

Methods. All determinations were made in duplicate. Urine urea nitrogen was determined by the manometric urease method of Van Slyke.¹² Whole blood urea nitrogen was estimated by the hypobromite method of Van Slyke and Kugel¹⁸ or by the aëration and titration method of Cullen and Van Slyke.¹² Because the hypobromite method yields only 95% of the urea nitrogen and a variable amount from amino-acids, necessitating the use of an empirical correction, its reliability for low values seemed questionable. A series of determinations was therefore carried out by both methods on the same samples. The average difference in the two methods in 15 determinations on bloods containing 3 to 9 mg. urea nitrogen per 100 cc. was 0.36 mg. per 100 cc. There was no systematic difference; in 9 instances the hypobromite method gave the higher value, in 4 the lower.

In 8 comparisons on bloods containing above 10 mg. urea nitrogen per 100 cc. the average difference was 0.23 mg. per 100 cc. On the basis of this comparison, it was decided that the hypobromite method, even in the low range, gave results sufficiently accurate for the purpose of this study. The length of urine collection periods was usually 1 hour; with high urine flows occasionally 45 or 30 minutes. When there was any doubt concerning the ability to empty the bladder, the patient was catheterized. Except in studying the effect of meals, collections were made at an approximately constant diuresis or on a falling curve, and under basal conditions.

Inulin was determined in plasma and urine by the method of Corcoran and Page.⁴ Cardiac output was estimated from intra-arterial pressure curves and pulse wave velocities by Bazett's² method. Total urine nitrogen was determined by micro-Kjeldahl.

Subject L, age 28, was observed on diets containing 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.4, 2.7 and 3.8 gm. of protein per kilo which furnished from 19 to 240 gm. of protein. The total calorie intake was kept approximately constant. Sufficient time was allowed on each diet for the establishment of nitrogen equilibrium, as indicated by total urinary nitrogen, before clearances were determined. Four to nine maximum clearances, each of $\frac{1}{2}$ hour, were obtained under basal conditions. Blood was drawn at the beginning and end of the collections, and interpolated values used in the calculations. Estimations of the basal metabolic rate were made at each level of protein intake, of cardiac output on alternate diets, and of inulin clearance on the lowest and highest protein intake (see Table 1).

TABLE 1.—CHANGES IN MAXIMUM UREA CLEARANCE, BASAL METABOLISM, AND CARDIAC OUTPUT WITH DIETARY PROTEIN.

Subject L., age 28, height 163 cm., weight 64 kg.

Protein.		Mean fast- ing B.U.N., mg./100 cc.	Mean max. urea clearance, cc./min.	Mean inulin clearance, cc./min.	Urinary nitrogen, gm./24 hrs.	B.M.R., %.	Cardiac output, l./min.
Gm./kg.	Total.						
0.3	19	4.0	54.8	123	3.6	-14*	3.21
0.6	38	6.1	63.9	..	5.7	-21	
0.9	58	10.5	61.2	..	8.3	-13	
1.2	77	10.1	63.8	..	12.1	-18	
1.5	96	12.6	71.8	..	14.9	-15	3.36
1.8	115	12.9	68.6	..	17.3	-17	
2.4	150	17.1	75.3	144	22.5	-13	2.68
2.7	186	19.0	76.5	..	27.7		
3.6	230	17.9	77.0	..	35.3	-18	

* In spite of the persistently low basal metabolic rate, the subject showed no clinical or other laboratory evidence of hypothyroidism.

While there was considerable variation in the individual clearances, the mean clearance on each diet shows a significant correlation with the protein intake. There was no detectable change in basal metabolic rate, nor in basal cardiac output. Inulin clearance, assumed to represent the volume of glomerular filtrate, was somewhat greater on the higher protein diet. The urea/inulin clearance ratio was not significantly changed, being 0.45 on the low protein diet and 0.52 on the high.

Chart 1 shows a progressive increase in mean clearance from the lowest protein diet up to one containing about 100 gm. of protein. Diets containing more protein did not give any further increase in clearance. There is enough variation in the individual clearance periods to make the difference in means between on any two adjacent diets not statistically significant, nor is the difference between the mean on the 0.6 and 1.5 gm. per kilo diets significant. The

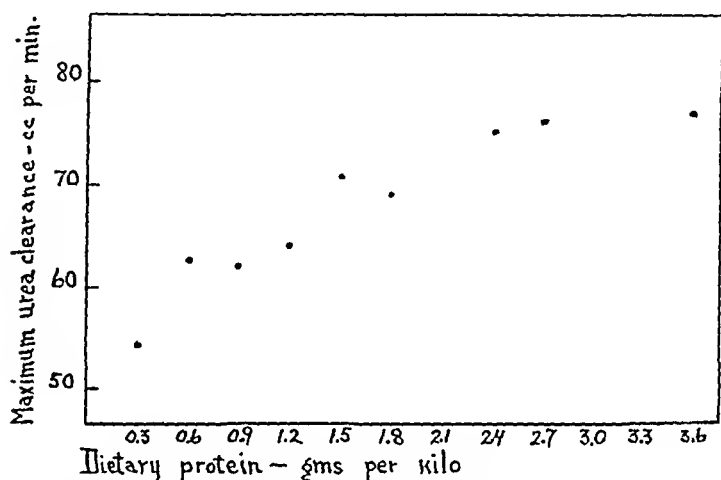


CHART 1.—Relation between dietary protein and mean fasting maximum urea clearance in Subject L.

difference between the mean clearance on the 0.3- and on the 1.5-gm. diets, 12.99 ± 3.79 cc. is significant according to Fisher's⁵ test for t as well as the difference between the 0.6- and 2.4-gm. diets (11.50 ± 4.04). Taking all the points on the ascending part of the curve (0.3 to 2.1 gm./kg.) the correlation coefficient between protein intake and mean clearance is 0.860.

Similar, but less complete, studies were made on another subject, B, age 16, weight 64.4 kilo. On a diet containing 20 gm. protein (or 0.3 gm./kilo) his mean basal maximum urea clearance was 57.33 cc. per minute with a blood urea nitrogen of 5 mg. per 100 cc., while on a diet containing 40 gm. protein, or 0.6 gm. per kilo, his blood urea nitrogen rose to 7.5 mg. per 100 cc. and his mean clearance to 65.82 cc. per minute. The difference, 8.49 ± 3.38 , is significant. In this subject, however, there was no further rise in clearances on a diet of 100 gm. or 1.5 gm. per kilo. This, however, is open to question for although he had been on the diet for 12 days, he was still not in nitrogen equilibrium. Mean inulin clearance rose significantly from 105 cc. per minute on the low diet to 130 cc. on the highest, while the urea inulin ratio remained unchanged (0.54 and 0.49). As in the first subject, there was no increase in estimated basal metabolic rate or cardiac output.

These data raise two questions: what is the explanation of the increasing clearance with diets from 19 to 100 gm. of protein; and why does the clearance not continue to rise with higher diets?

The data on dogs are consistent with the belief that the increased clearances may be attributed to an increased renal bloodflow. The increased inulin clearance in these subjects are consistent with the same interpretation, provided the inulin extraction ratio remained constant. But since there was no measurable change in cardiac output or basal metabolism, the increased renal bloodflow may have been brought about by intrarenal vascular adjustments rather than by an increase in cardiac output. Some such mechanism is also suggested by the difference between the changes in clearance due to diet and those due to hyperthyroidism. Two patients with hyperthyroidism were studied before treatment and after recovery from thyroidectomy. In both, basal metabolic rate, cardiac output, and inulin and urea clearances fell after operation, but the fraction of the cardiac output represented by the inulin clearance was unchanged. The level of blood urea nitrogen in 1 patient was 7.6 mg. per 100 cc. before and 4.4 mg. per 100 cc. after operation, in the other 14.9 and 12.7. Both patients were receiving a diet containing 100 gm. protein when the clearances were determined. That is, in hyperthyroidism, the increased renal blood flow and clearances apparently are a reflection of the increased metabolism and cardiac output, while in normal subjects changes in metabolic rate and cardiac output could not be detected with alterations in diet. For while in a normal subject protein overfeeding for a number of days causes a cumulative increase in the specific dynamic action of protein, the effect lasts only so long as the food is being absorbed, and does not give an increase in the fasting metabolic rate.¹³ Since these increased clearances were observed under basal conditions, they cannot be attributed to increased metabolism from the previous day's protein intake. Nor can the increased clearance on high protein diets be attributed to the elevated blood urea nitrogen. Möller, McIntosh, and Van Slyke,¹¹ and others have shown that raising the blood urea nitrogen from the normal range of 10 to 16 mg. per 100 cc. to two or three times as much by feeding urea had no effect on the clearance value. Cope,³ however, pointed out that to obtain by urea administration the same blood changes that are produced by low and high protein diets, it would be necessary to administer urea to a subject in nitrogen equilibrium on a low protein diet. Data of Fowwether⁶ suggested that under such conditions urea itself might be responsible for an increase in clearance. However, in Subject B while in nitrogen balance on a diet containing 19 gm. of protein with a fasting blood urea nitrogen of 6.2 mg. per 100 cc. neither the ingestion of 30 gm. of urea, which raised the blood level to 30.4, nor of 5 gm. every 4 hours for 2 days led to any increase in the maximum urea clearance. This seems to complete the evidence against urea.

of the 24 hours in which urine volume is above the augmentation limit. With a constant blood urea nitrogen an increase in urine volume to the augmentation limit increases urea excretion. Further increase has little or no effect, but an increase in the number of hours during which urea is excreted at a maximum rate increases the urea eliminated per day. This is born out by the fall in blood urea nitrogen during a series of clearances while fasting, in spite of the fact that the value of the clearance itself does not change.

TABLE 2.—CHANGES IN FASTING MAXIMUM UREA CLEARANCE WITH MODERATE ALTERATION IN PROTEIN INTAKE.

Subject.	Ht. Wt.	Protein, gm.	Mean B.U.N., mg./100 cc.	Mean clearance, cc./min.	Protein, gm.	Mean B.U.N., mg./100 cc.	Mean clearance, cc./min.
D . . .	173.5 56.4	40	6.7	51.4	100	14.9	60.5
M . . .	180.0 72.5	50	9.9	71.1	110	14.9	81.3
Br. . . .	172.0 77.0	50	9.5	77.8	130	15.7	86.3
B	171.0 65.4	40	7.9	65.8	100	10.1	63.3
R	181.0 72.7	20	4.0	93.5	150	10.2	111.1
McC. . .	177.5 61.2	30	4.1	65.0	150	13.8	76.7

Six additional subjects have also been studied on two diets: in 4, the low protein diet contained 40 to 50 gm., while in the other 2, it was reduced to 20 and 30 gm. The mean blood urea nitrogen and clearances of these subjects are shown in Table 2. The first 4 had fasting blood urea nitrogens above 6 mg. per 100 cc. on the low protein diet, and while the mean clearances on the high diets are elevated, in none of the 4 is the difference significant. The other 2 subjects had fasting blood urea nitrogens of 4 and 4.1 mg. per 100 cc. on diets of 20 and 30 gm. of protein, and showed a significant increase in clearance on 150-gm. protein diets. It would seem that while man, like the dog, shows a decreased urea clearance on low protein diets, that this only becomes significant when the protein intake is markedly restricted, and that variations in protein intake of ordinary diets, from 40 gm. up, need not be considered in determining the urea clearance as a test of kidney function. Cope,³ however, found that such changes in diet did make a difference in the standard clearance in nephritic subjects.

Chart 2 shows the relation between fasting blood urea nitrogen and protein intake in our data and that of Goldring, Razinsky, Greenblatt, and Cohen.^{7*} In normal subjects the fasting blood urea nitrogen furnishes a fairly reliable index of the level of protein metabolism over the usual range of diet. Variations in diet are probably an important factor in the wide spread usually given for

* Dr. Goldring kindly furnished the weights of his subjects and has allowed us to use his data.

the "normal" blood urea nitrogen. Since this does not fall below 6 mg. per 100 cc. as a rule until the protein intake is below 0.6 gm. per kilo or about 40 gm., the possibility that low maximum clearances are due to a low protein intake can probably be disregarded if the fasting blood urea nitrogen is 6 mg. per 100 cc. or above.

The effects of meals on maximum clearances in subjects on low and high protein diets are shown in Table 3. On each diet, the subjects were given meals corresponding to that diet. On a 40-gm. diet, B's mean clearance averages slightly higher with meals, but the difference is not significant ($P = 0.88$. P is the probability that a difference between the means as great as or greater than that observed would not be obtained by the operation of chance alone). With the higher protein diets both B and L showed a significantly higher mean clearance with meals ($P = >0.999$ and >0.999). Other data on 3 individuals observed throughout the day with meals corresponding to 40- and 100-gm. diets also showed increases after meals, more marked as would be expected when larger amounts of protein were ingested. It was frequently noted that in spite of a constant fluid intake the urine volume diminished immediately after a meal, so that "standard" rather than "maximum" clearances were obtained. This probably reflects diversion of blood to the intestinal tract during the process of digestion with consequent diminution in renal blood flow. The variability of a series of clearances without meals, however, is just as great as when the subject is fed. The average coefficient of variation for clearances with meals was 11.4% and 9.5% fasting. Considering all our data, it seems likely that a meal containing 10 gm. or less of protein will not significantly affect the maximum urea clearance.

The effect of larger protein meals on maximum urea clearance contrasts with MacKay's⁹ findings that meals are without effect on the "standard" clearance. MacKay's conclusion, however, was based on variations throughout the day in 4 subjects who received meals, without equal periods of observation fasting, and on 1 normal subject observed from 8 to 10 A.M. on 3 days with and 3 days without breakfast. No data are given on the amount of protein taken by this subject.

Table 4 shows the effect of a single large protein meal (114 and 109 gm.) on the clearances when the subject had been on low and high protein diets. On the low diet, there is little change for 6 hours and then a sudden sharp rise during the last two periods of observation. The clearances remained low while the blood urea nitrogen was rising, and did not rise until after it had begun to fall. On the higher diet, there was an immediate and progressive rise for a period of 6 hours. During all this time, the blood urea nitrogen was rising. These increases in clearances may probably be attributed to the specific dynamic action of the protein and the accompanying increase in metabolic rate and cardiac output, so that the increase is similar to that found in hyperthyroidism rather than to the change

TABLE 3.—THE EFFECT OF MEALS ON THE MAXIMUM UREA CLEARANCE.

Subject B, height 171 cm., weight 65.4 kg., 200 cc. H₂O per hour.40 gm. diet with meals; 13 gm. protein at
8 A.M., 12, 5 P.M.

40 gm. diet fasting.

Time.	Urine vol., cc./min.	Blood urea N, mg./100 cc.	Clear- ance, cc./min.	Time.	Urine vol., cc./min.	Blood urea N, mg./100 cc.	Clear- ance, cc./min.
7:29				7:31			
8:28	6.61	7.9	66.7	8:30	3.60	7.2	62.1
9:20	1.90	7.8	*67.9	9:28	8.72	7.2	78.4
9:51	5.36	7.7	61.7	10:25	9.36	7.2	78.1
10:26	8.92	7.6	67.2	11:30	5.57	7.2	68.0
11:11	5.16	7.5	62.0	12:30	2.47	7.2	67.3
11:54	4.33	7.4	67.3	1:30	5.90	7.2	71.6
12:30	3.78	7.3	68.5	2:26	6.23	7.2	72.3
1:10	4.60	7.2	64.5	3:30	3.56	7.2	62.7
1:40	8.77	7.1	67.9	4:28	6.98	7.2	67.4
				5:21	3.13	7.3	57.0
				6:27	1.88	7.3	*48.0
				7:29	4.52	7.3	106.6
				8:30	4.51	7.3	64.6
Mean:		65.82 σ = 2.62					71.30 σ = 12.73

* Standard clearance, not included in averages.

100 gm. diet with meals; 30 gm. protein at
100 gm. diet fasting. 8 A.M., 30 at 11:45 A.M., 40 at 5 P.M.

Time.	Urine vol., cc./min.	Blood urea N, mg./100 cc.	Clear- ance, cc./min.	Time.	Urine vol., cc./min.	Blood urea N, mg./100 cc.	Clear- ance, cc./min.
8:30				7:30			
9:01	9.02	10.1	72.8	8:32	6.34	9.6	78.6
9:30	10.57	10.1	64.8	9:27	7.78	9.9	81.4
10:01	7.39	10.1	61.2	10:30	3.49	10.1	81.3
10:30	7.83	10.1	69.0	11:33	4.13	10.4	77.1
11:00	6.80	9.9	61.3	12:48	1.43	10.5	*63.2
11:30	6.14	9.8	52.5	1:30	6.62	10.5	82.0
12:00	5.67	9.6	58.3	2:30	2.30	10.6	82.7
12:30	4.67	9.5	54.0	3:15	3.02	10.6	80.3
1:00	4.77	9.3	76.7	4:00	4.22	11.2	82.8
				4:45	2.47	11.8	68.4
				5:30	3.02	12.5	81.8
				6:15	3.38	13.1	69.2
				7:00	3.07	13.7	81.0
Mean:		63.28 σ = 8.209					78.73 σ = 4.998

* Standard clearance, not included in averages.

Subject L., height 163 cm., weight 64 kg., 300 cc. H₂O per hour.75 gm. diet with meals; 20 gm. protein at
8:20 A.M., 22 at 12, 33 at 5 P.M.

75 gm. diet fasting.

Time.	Urine vol., cc./min.	Blood urea N, mg./100 cc.	Clear- ance, cc./min.	Time.	Urine vol., cc./min.	Blood urea N, mg./100 cc.	Clear- ance, cc./min.
8:10				6:55			
8:42	5.28	9.5	59.4	7:27	8.04	11.6	69.6
9:09	7.59	9.5	69.0	7:53	9.31	11.6	66.9
9:36	7.64	9.5	62.5	8:20	lost		
10:06	6.87	9.5	63.0	8:46	9.34	11.6	73.6
10:35	7.86	9.5	68.0	9:15	10.17	11.6	86.0
11:00	6.40	9.5	59.7	9:45	10.66	11.6	78.9
11:30	7.30	9.5	66.0	10:15	7.40	11.6	78.2
11:58	7.86	9.5	71.4	10:45	9.50	11.6	83.8
12:28	5.80	9.5	61.7	11:15	8.23	11.6	78.2
				11:45	7.50	11.6	73.2
				12:28	7.30	11.6	72.4
				1:00	2.13	11.6	62.6
				1:30	3.17	11.6	82.0
				2:00	9.46	11.6	89.9
				2:30	9.94	11.6	86.4
				3:00	8.14	11.6	78.8
Average:		64.52 σ = 4.29					77.36 σ = 6.91

in basal clearances found on low and high diets. The lag in clearance increase on the low protein diet is more consistent with Lusk's⁸ finding that after a low protein diet the specific dynamic action of proteins is disturbed, than with the findings of Strang and McCluggage¹⁷ that the specific dynamic action is unaffected as long as the subject is in nitrogen equilibrium. This subject was in nitrogen equilibrium on both occasions.

TABLE 4.—EFFECT OF A SINGLE HIGH PROTEIN MEAL UPON CLEARANCES IN SUBJECT L.

Previous diet = 19 gm. From 9:30–10:00
(meal containing 114 gm. protein).

Time.	Urine vol., cc./min.	B.U.N., mg./100 cc.	Clear- ance, cc.
8:00– 8:34	8.51	5.38	63.1
8:30– 9:04	9.08	5.35	68.4
9:00– 9:33	10.71	5.32	55.2
9:30–10:30	3.98	6.08	55.5
10:30–11:30	4.60	7.17	72.1
11:30–12:30	4.10	12.16	51.0
12:30– 1:30	3.92	17.14	42.2
1:30– 2:30	4.26	18.34	54.6
2:30– 3:30	7.03	19.54	46.5
3:30– 4:30	5.70	16.09	68.3
4:30– 5:30	10.17	12.64	100.0

Previous diet = 120 gm. From 9:00–10:00
(meal containing 108 gm. protein).

Time.	Urine vol., cc./min.	B.U.N., mg./100 cc.	Clear- ance, cc.
7:00– 8:00	8.21	12.14	60.3
8:00– 9:00	11.58	12.28	79.9
9:00–10:00	4.68	12.22	72.2
10:00–11:00	3.15	12.53	78.2
11:00–12:00	3.48	13.79	88.7
12:00– 1:00	5.38	14.92	90.1
1:00– 2:00	4.55	16.58	95.8
2:00– 3:00	9.54	17.95	102.8
3:00– 4:00	9.25	18.75	99.6
4:00– 5:00	8.82	19.20	103.1
5:00– 6:00	11.74	19.39	102.8

Summary. In a normal subject in nitrogen equilibrium there is a progressive increase in maximum urea clearance when dietary protein is increased from 0.3 to 2.4 gm. per kilo but no further increase in clearance with greater protein intake. This was not accompanied by detectable change in basal metabolic rate or cardiac output. The urea/inulin clearance ratio was not changed.

Fasting blood urea nitrogen also increases progressively with the dietary protein up to about the same level of protein intake, and is not further increased by higher protein diets.

The increased clearance on high protein diet is not due to the elevated blood urea nitrogen. It is suggested that it may be brought about by increased renal blood flow due to intrarenal vascular adjustments mediated through the higher concentration of amino-acids on high protein diets.

Progressive increase in blood urea nitrogen on high protein diets is apparently prevented by increased urine output, giving maximum clearances for a greater part of the 24 hours.

The effect of meals on maximum urea clearance varies with the amount of protein ingested and with the previous level of nitrogen intake. While the mean clearance on a day when meals are eaten is higher than when fasting, the variability is just as great and the difference not sufficient to require that clearances be determined fasting for routine work.

For the greatest precision, however, maximum urea clearances should be determined with the subject fasting, and cognizance taken of the previous diet. Since, however, there is little change in clearance with diets of 40 gm. protein and above, if the fasting

blood urea nitrogen is above 6 mg. per 100 cc. it can be assumed that the previous diet has contained enough protein to give maximum clearances.

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BRONCHOPNEUMONIA OF UNKNOWN ETIOLOGY IN A GIRLS' SCHOOL.*

By WORTH B. DANIELS, M.D.,

CLINICAL PROFESSOR OF MEDICINE, GEORGETOWN UNIVERSITY MEDICAL SCHOOL,
WASHINGTON, D. C.

(From the Medical Service of the Emergency Hospital.)

DURING a 6 weeks' period from November 25, 1940, to January 7, 1941, 13 cases of pneumonia occurred in a girls' school in northern Virginia. The school consists of approximately 90 girls, giving a case incidence of 14.4%.

Epidemiology. The school is situated at some distance from any town with but little contact with people from the outside. However, on November 14 the entire student body went to a church fair in a nearby village; and on November 20, Thanksgiving Day, a general homecoming for alumnae and friends was held at the school. At this time more than 500 people came to the school and in the afternoon groups of 12 to 15 girls visited various houses in the neighborhood. The girls range from 13 to 18 years of age. They live in four separate houses according to their class in school. The fourth year students live and eat in a house of their own, $\frac{1}{4}$ mile from the main school. In this group, no person was affected. In addition to the student body, there are about 80 members of the faculty and service force, none of whom contracted the disease. The local physicians in this area met with no similar cases in their practices outside the school. The girls in the three lower classes eat in a

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common dining room but there are no permanent seating arrangements. In study hall and assembly girls of all four classes come together. All the students sleep on sleeping porches, 2 to 7 on a porch. On one porch with 7 girls, 4 of them contracted the disease. There is only 1 instance of room-mates affected. Four cases occurred in girls using the same bathrooms. The cases developed in the following sequence: November 25, 2 cases; November 27, 1 case; November 29, 1 case; December 2, 2 cases; thereafter 1 case on December 4, 8, 9, 12, 18, 21, and January 7. None of the physicians or nurses attending these patients developed the disease. The grandmother of Case 7, who visited the patient in the hospital, developed pneumonia 11 days later. She was said to have pneumococcus Type XIV lobar pneumonia with leukocytosis and recovered rapidly after treatment with sulfathiazol, begun on the fifth day of this illness. The room-mate of Case 11 developed pneumonia in Colorado Springs during the Christmas holidays. Her physician has answered none of my letters of inquiry. The school understood that the physician called this a pneumococcus pneumonia. We can draw no definite conclusions about the incubation period. However, the sequence in which new cases developed suggested that it might range between 7 and 22 days. In the first year house cases occurred on the 19th, 20th and 22d days after Case 1 became ill. Case 12 became ill 20 days after leaving school for Christmas. While at home she had no contact with any person from the school. In the other two houses cases developed from 2 to 19 days after the original case occurred. Kneeland and Smetana⁹ thought that the incubation period of their cases was between 2 and 3 weeks. Longcope's¹⁰ cases seem to indicate a similar period of incubation. It seems apparent that this outbreak was due to person to person contact.

Clinical Picture. The onset in this group of cases was, as a rule, abrupt. Headache was the presenting symptom in 10 of the 13 cases. Sore throat was complained of in 11 instances, but within 48 hours after onset this symptom cleared. Shortly after onset in all instances a characteristic, harsh, non-productive cough developed which was frequently paroxysmal. Change in position and examination of the chest produced paroxysms of coughing. Three patients complained of chilliness and 1 had an actual shaking chill. Substernal tightness and chest soreness were present in a few cases but actual chest pain was conspicuously absent. Fever occurred early in most cases, mounting to its maximum level of 100° F. to 105° F. after a few days. It was swinging in type, generally highest in the afternoon. In 1 case fever above 99° F. was present for only 1 day. The longest febrile period was 14 days, average about 8 days. The illness in these girls was definitely mild, except in 1 case where significant cyanosis and signs of toxicity occurred. This case, in its severity, would fall into Group II of Longcope's classification.¹⁰

There was a complete absence of influenza-like symptoms preceding and during the disease.

At the onset, physical examination revealed no abnormality in the majority of instances, though occasionally there was a slight injection of the pharynx. The pulse and respiration were, as a rule, only slightly elevated. Abnormal signs in the chest appeared anywhere from the third to the tenth day of the illness. At first these consisted of a few localized subcrepitant râles, most frequently heard in one or the other interscapular region without change of percussion note or breath sounds. Gradually impairment of percussion note developed, associated with suppression of breath sounds and an increase in large moist râles. The signs in the majority of instances slowly involved the major part of the affected lobe, though some cases showed no increase in the original signs. In only 3 patients did bronchial breathing develop. Restriction of movement of the involved chest on inspiration was striking in 3 individuals whose other lung signs were minimal. As the disease terminated, diffuse moisture often developed over the entire lobe and in several instances râles were numerous over the entire affected side of the chest. Clearing of physical signs, particularly dullness, was rapid, though a few râles were still audible in all cases on discharge.

Laboratory Findings. Blood cultures were done in 7 cases and none showed any growth. Lack of sputum was striking and made examination possible in only 4 cases. Pneumococcus Type XIX was found in 1 case and Type VI in another. However, *Micro. catarrhalis* and *Staph. albus* and *aureus* and *Strep. viridans* were the predominant organisms. *Blood picture:* All cases showed leukopenia or normal counts. The differential counts were normal except in 2 instances in which there was a moderate lymphocytosis. The leukocyte count was done at frequent intervals but leukocytosis did not occur toward the termination of the disease as reported by Longcope¹⁰ and Murray.¹³

Roentgen Ray Examination. Roentgen ray films made early in the disease may show only slight infiltration in the region of the hilus associated with accentuation of the bronchial markings extending into one of the lobes. Gradually a definite soft infiltration of the lung parenchyma develops. This as a rule does not involve the entire lobe nor does it develop the density ordinarily seen in true lobar pneumonia. Sometimes this infiltration involves a wedge leading to the periphery. In 4 of our cases Roentgen ray films showed a spread to another lobe prior to the development of physical signs. This spread was usually not accompanied by increase in severity of the illness. Clearing of the infiltration took place rapidly after the disappearance of fever so that little or no residual shadow was left in the film.

Complications. During convalescence 1 patient developed nausea and vomiting with pain in the right lower quadrant simulating

acute appendicitis but disappearing in 36 hours. No nervous system symptoms as described by Reimann¹⁴ occurred in this group.

Treatment. Four cases were treated with sulfathiazol without beneficial effect, so the drug was discontinued. In the other cases treatment was purely symptomatic.

Prognosis. Convalescence in this group was extremely rapid. There were no deaths.

Case Reports. Table 1 summarizes the significant findings in the 13 cases. None of these patients had heart disease or any other chronic illness. The past histories in all these young girls was of no importance in their illness. None had suffered with any disease aside from the simpler illnesses of childhood. Case 1 is reported in detail to give a clear picture of the disease; the other cases are reported in brief.

TABLE 1.

Case No.	Date of onset.	Fever.			Lung involvement.	Leukocytes.	Polys., %.	Blood culture.	Animal inoculation.	Sputum.
		Maximum.	Character.	Duration, days.						
1	11-29-40	103°	Swinging	14	L.U.L.: L.L.L.	7,100	67	No growth	Negative	<i>Micro. Catarrhalis</i> ; <i>Staph. albus</i> ; pneumococcus Type VI.
2	11-22-40	102°	Swinging	12	R.L.L.	6,000	60	Not made	Not done	None obtainable.
3	11-25-40	104°	Swinging	8	R.L.L.	6,900	64	No growth	Not done	<i>Micro. catarrhalis</i> ; <i>Staph. albus</i>
4	11-25-40	103°	Swinging	7	L.L.L.	Not done	Not done	Not done	Not done	Not examined.
5	12- 2-40	100°	Swinging	14	R.L.L.	Not done	Not done	Not done	Not done	Not examined.
6	12- 2-40	102°	Swinging	15	L.L.L.	11,000	59	No growth	Negative	None obtainable.
7	12- 4-40	102°	Swinging	13	L.L.L.	10,000	62	No growth	Negative	None obtainable.
8	12- 8-40	105°	Swinging	8	R.L.L.	6,400	70	No growth	Negative	Not obtainable.
9	12- 5-40	101°	Swinging	9	L.U.L.: R.M.L.	8,500	72	No growth	Negative	None obtainable.
10	12-12-40	99°	Flat	1	R.M.L.	5,100	55	Not made	Negative	<i>Micro. catarrhalis</i> ; <i>Strep. hemolyticus</i> ; pneumoc. Type XIX.
11	12-18-40	102°	Swinging	7	R.L.L.: L.L.L.	5,500	60	Not made	Not done	None obtainable.
12	1- 7-41	102.5°	Swinging	14	R.L.L.	10,000	75	Not made	Not done	<i>Staph. albus</i> ; <i>Strep. hemolyticus</i> ; <i>Micro. catarrhalis</i> .
13	12-21-40	101°	Swinging	14	L.L.L.	Not done	Not made	Not made	Not done	Not examined.

CASE 1.—M. L. S., aged 14, became ill with headache, nasal congestion and sore throat associated with fever of 100°. The following day an unproductive cough developed but the sore throat cleared. While in the school infirmary, she ran a swinging temperature ranging from 99° to 103° (Fig. 1). On admission to the hospital on the eighth day of the illness her temperature was 101°, pulse 120, respirations 36. The patient appeared acutely ill and coughed persistently in a queer dry, metallic way. Any change of position initiated cough and chest examination produced marked paroxysms. There was moderate cyanosis of the lips and nail beds. There was a striking lag of the left upper chest on inspiration associated with moderate dullness and numerous moist, bubbling râles in this region. There was slight nasal congestion. No sputum could be obtained for

typing. A Roentgen ray film on the eighth day showed "an area of infiltration on the left side between the level of the second and fourth ribs anteriorly" (Fig. 2). Sulfathiazol was given in dosage adequate to produce a blood level of 5 mg. per 100 cc. On the eighth day of the illness, pneumococcus Type VI was obtained from a mouse which had been injected

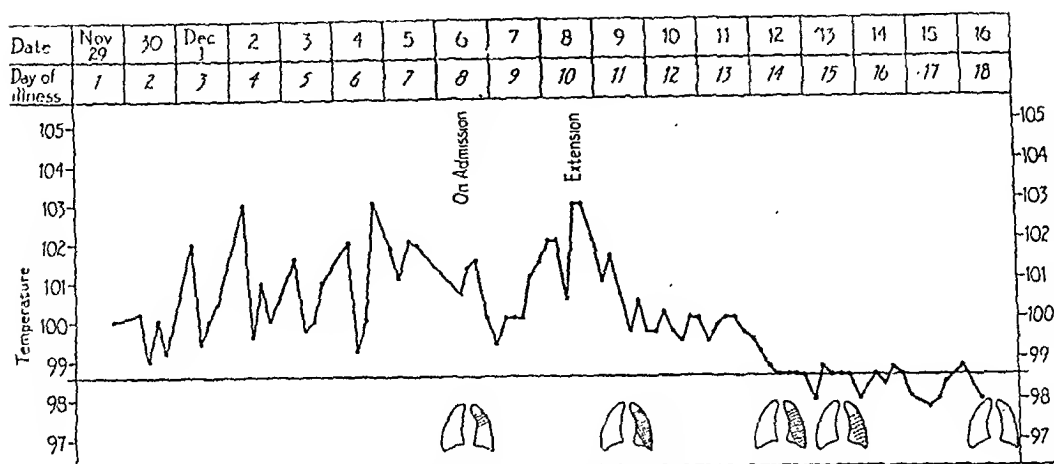


FIG. 1.—Case 1. Graphic record of temperature and lung findings.

with sputum intraperitoneally. Culture also showed *Micro. catarrhalis* and *Staph. albus*. On the tenth day of the illness the patient was definitely worse and the temperature rose to 103°. At this time impairment of percussion with scattered suberepitant râles was noted over the left lower lobe posteriorly and distant bronchial breathing had developed over the left upper lobe. A Roentgen ray film showed an extension of the infiltration



FIG. 2.—Case 1. Roentgen ray film of chest on eighth day of illness.

in the left upper lobe and the development of an inflammatory process in the left lower lobe (Fig. 3). After 3 days of sulfathiazol, the drug was stopped because it had been ineffectual and because on this day 2 other students from the school came under my care with the same illness. This made me feel that "Pneumonia-X" was the cause of the patient's illness. Improvement gradually occurred and the temperature reached normal on the fourteenth day of the illness. At this time pneumococcus Type VI was again cultured from the sputum. Roentgen ray examination on the

eighteenth day showed practically complete clearing (Fig. 4). Moist râles were still present over the entire left chest. There were, too, numerous sibilant and sonorous râles over the right chest. Convalescence was uneventful.



FIG. 3.—Case 1. Roentgen ray film of chest on tenth day of illness.

CASE 2.—(Courtesy of Dr. Montgomery Blair.) M. M., aged 15, developed headache, sore throat and fever shortly followed by persistent dry cough, often paroxysmal. On the tenth day râles were heard at both bases and a Roentgen ray showed a fairly extensive pneumonic infiltration involving the right lower lobe, with mild peribronchial infiltration on the

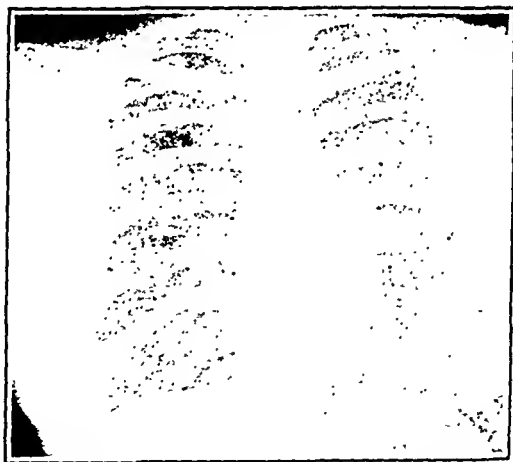


FIG. 4.—Case 1. Roentgen ray film of chest on eighteenth day of illness.

left (Fig. 5). Her illness was mild and by the seventeenth day the chest examination and Roentgen ray films showed no abnormality.

CASE 3.—(Courtesy of Dr. John Minor.) H. S., aged 17, became suddenly ill with headache, chilliness and fever. Dry cough developed on the second day. On the fourth day slight dullness and bronchial breathing were found over the right base posteriorly and later numerous moist râles were heard. Roentgen ray showed a diffuse opacity over the right lower

lobe (Fig. 6), but by the fourteenth day very little infiltration was noted in the film. This patient was the room-mate of Case 6 and slept on the porch with Cases 6, 9 and 10. She used the same bathroom with Cases 6 and 10.

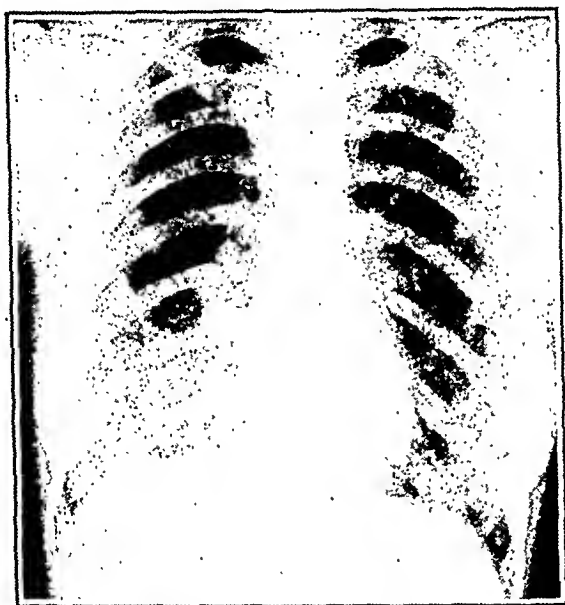


FIG. 5.—Case 2. Roentgen ray film of chest on tenth day of illness.

CASE 4.—(Courtesy of Dr. Homer A. Spitler.) W. M., aged 16, developed headache with mild fever, and on the following day, sore throat and dry, metallic cough. Late in the disease moist râles were noted over one base posteriorly. No Roentgen ray was made. Her illness was mild so that she was not admitted to the hospital.

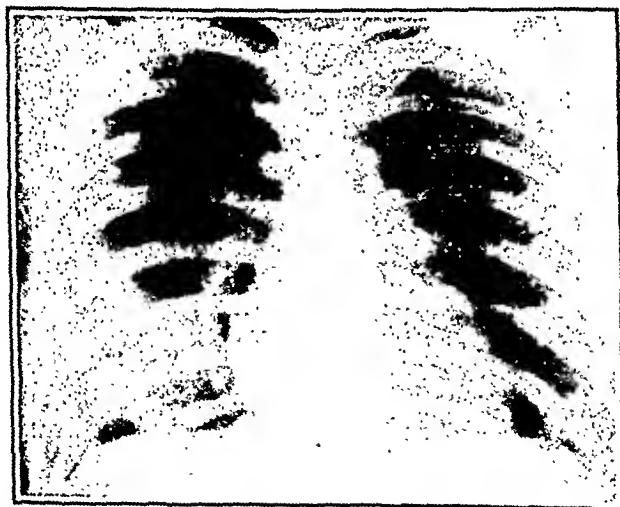


FIG. 6.—Case 3. Roentgen ray film of chest on fourth day of illness.

CASE 5.—C. D., aged 16, began with headache, malaise and cough. Persistent dry, metallic cough with very mild fever continued. When first seen on the eleventh day of the disease there was dullness, distant breath sounds and moist râles at the right base posteriorly. During con-

valescence she developed right lower quadrant pain and tenderness with nausea and vomiting. This cleared in 36 hours. Roentgen ray at this time showed mild peribronchial infiltration on both sides.



FIG. 7.—Case 6. Roentgen ray film of chest on fifth day of illness.

CASE 6.—V. J., aged 16, became suddenly ill with headache, malaise, sore throat, cough and fever. Her cough was persistent, dry and metallic. On the fifth day limitation of motion, dullness and moist râles developed over the left lower lobe. Roentgen ray films showed a slight infiltration in the mid-portion of the left chest (Fig. 7). This had completely cleared

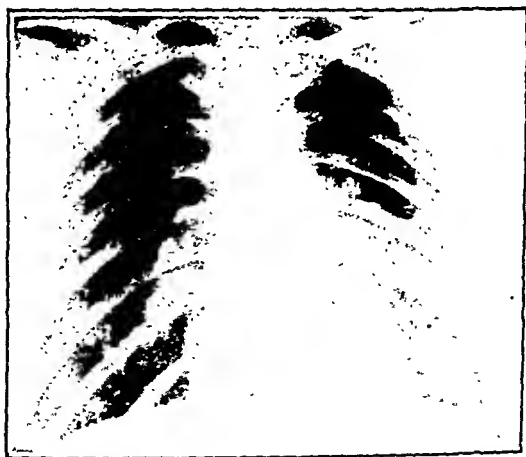


FIG. 8. Case 7. Roentgen ray film of chest on seventh day of illness.

in films taken on the twelfth day of the illness. This patient was the room-mate of Case 3, slept on the porch with Cases 3, 9, and 10, and used the same bathroom with Cases 3 and 10. Her grandmother developed

pneumonia 11 days after visiting her in the hospital. This was said to be due to pneumococcus Type XIV.
 CASE 7.—C. H., aged 17, started with sore throat, headache, cough and fever. The dry cough persisted. On the fourth day there were no chest signs but the Roentgen ray showed a small area of infiltration extending out from the right hilum. By the eighth day râles had developed in the

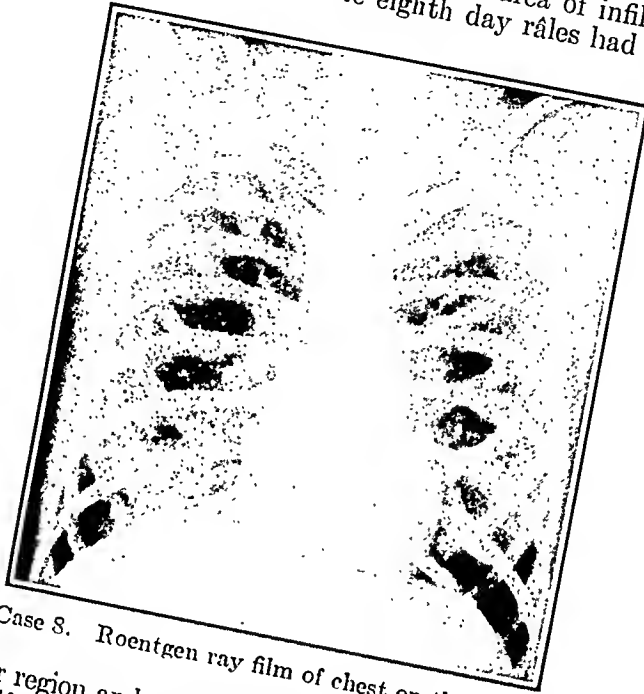


FIG. 9.—Case 8. Roentgen ray film of chest on third day of illness. left interscapular region and a film showed a moderate infiltration throughout the lower half of the left lung (Fig. 8). Later impairment, suppression of breath sounds and râles developed in this area. On the sixteenth day the Roentgen ray showed almost complete clearing.

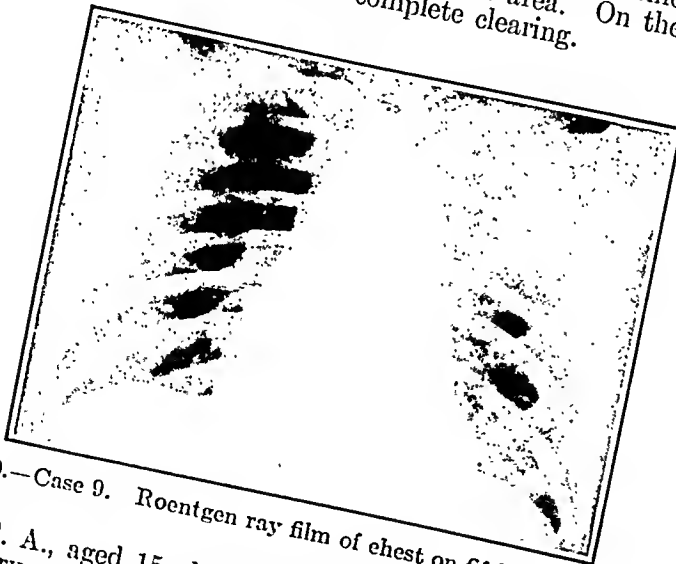


FIG. 10.—Case 9. Roentgen ray film of chest on fifth day of illness.

CASE 8.—E. A., aged 15, developed headache, malaise and sore throat followed by dry, non-productive cough. Her temperature was high but she was only mildly ill. On the third day impairment of percussion and

râles developed at the extreme right base, gradually spreading over the entire lobe. The film showed a soft infiltration throughout this area (Fig. 9) but by the tenth day this had largely cleared.

CASE 9.—M. C., aged 17, became ill insidiously with malaise and sore throat. On the third day, dry, non-productive cough and fever had developed. By the fifth day there was a marked lag of the left upper chest on inspiration associated with faint impairment but no râles. Later bronchial breathing developed in this area and the pneumonia spread to the right lung as indicated by râles in the right interscapular region. A film on the eleventh day showed a rather dense infiltration in the left upper lobe with faint infiltration in the right lower lobe (Fig. 10). This patient slept on the porch with Cases 3, 6 and 10.

CASE 10.—E. V., aged 15, gradually developed hoarseness and dry cough without fever. On the third day fever of 101° occurred but thereafter never rose above 99° . There were no chest signs until the fourth day when a few râles developed in the right interseapular region. At this time a Roentgen ray film showed a slight infiltration in the mid-portion of the right chest (Fig. 11). On the ninth day this had cleared markedly, but sibilant râles were still heard over the entire right chest.



FIG. 11.—Case 10. Roentgen ray film of chest on fourth day of illness.

CASE 11.—(Courtesy of Dr. John Diven.) A. H., aged 14, developed fever with no other symptoms on arriving home for the Christmas holidays. She later developed a dry non-productive cough with impairment over the left and then the right lower lobes, associated with suppressed breath sounds and a few scattered râles. A Roentgen ray film on the fifth day showed an infiltration involving portions of both lower lobes (Fig. 12). By the thirteenth day this had almost cleared. Her room-mate developed pneumonia of unknown character while away from the school at Christmas.

CASE 12.—J. B., aged 14, developed coryza, hoarseness, cough and slight fever on the day she returned to school after the Christmas holidays. Twenty days had elapsed since she had been in contact with any girl from the school. Her cough was mildly productive and there was nausea, vomiting and insomnia. On the tenth day râles developed in the right inter-

scapular region with the gradual development of moderate dullness, suppression and râles over the right lower lobe. Roentgen ray on the seventh day showed mild peribronchial infiltration extending into the right lower lobe, and by the ninth day, there was slight but definite infiltration there.

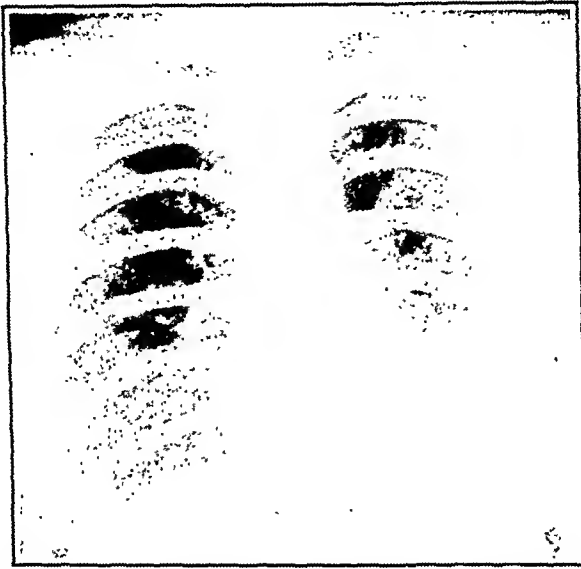


FIG. 12.—Case 11. Roentgen ray film of chest on sixth day of illness.

CASE 13.—(Courtesy of Dr. Walter F. Davey.) J. C., aged 15, had a gradual onset with malaise, general aching and fever while away from school for the Christmas holidays. Persistent dry, hacking cough began and later became productive of mucopurulent sputum. Late in the disease a few râles became audible at the bases.

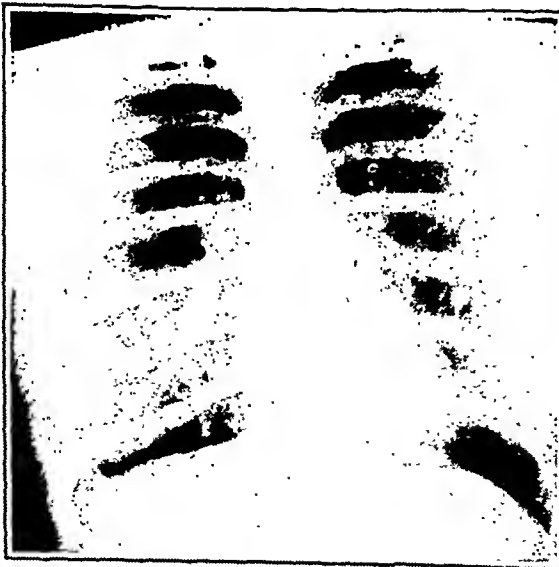


FIG. 13.—Case 12. Roentgen ray film of chest on ninth day of illness.

Discussion. This group of cases is strikingly similar to those reported by Bowen,³ Gallagher,⁷ Allen,¹ and others.^{8,11,12,16,17} The

case incidence in a brief period is greater in this outbreak than in any we have seen previously reported. This epidemic differs from that described by Reimann and Havens¹⁵ and others in that the patients did not show evidence of a grippe-like infection prior to the onset of lung involvement. During the period when these cases occurred the school was notably free of common colds and other upper respiratory infections.

The diagnosis of isolated cases of this disease may be extremely difficult when there is no epidemic. It might be well to repeat here the features that differentiate this entity from true lobar pneumonia. 1, The onset is usually mild without chill or chest pain. 2, The cough is dry, metallic, non-productive and often paroxysmal. It is so characteristic that after hearing it in the first few patients one could almost make a diagnosis in the later cases from the nature of the cough. 3, If sputum can be obtained it is not rusty and does not consistently contain pneumococci. 4, Leukocytosis with polymorphonuclear increase is absent. 5, Herpes does not occur. 6, The illness is usually mild and not accompanied by toxemia. 7, The fever is swinging in character. 8, There is a paucity of chest findings and rarely evidence of complete lobar solidification. 9, The areas of infiltration shown in the roentgenograms are less dense and do not as a rule involve the entire lobe. The films, however, show more involvement than physical examination would lead one to expect. 10, This disease is more apt to occur in mid-winter than in late winter and spring. 11, It is definitely more communicable. 12, Chemotherapy is of no value.

It was suggested by Bock² in 1938 that the great majority of these cases represented virus pneumonia. Reimann¹⁴ obtained a filterable virus from the blood of 1 patient and from the nasopharyngeal washings of another. A lung inflammation in experimental animals was produced with this agent. However, after several passages, the virus was lost. In 1940, during an outbreak of this disease at the National Institute of Health in Washington, D. C., Dyer and Topping⁵ isolated a rickettsia from the blood and nasopharyngeal washings of 3 patients. This they identified as the same rickettsia isolated by Burnett⁴ in 1937 in "Q" fever. Weir and Horsfall¹⁸ recently reported the isolation of a virus from the throat washings of cases of this type. This virus when inoculated into the mongoose produces pulmonary consolidation. It was not pathogenic for various other animals. The serum of human beings who had recovered from this disease was capable of protecting the mongoose against infection with this virus.

Dyer and Topping inoculated mice, guinea pigs and the chorio-allantoic membrane of hen's eggs with blood and pharyngeal washings from 6 of our cases. No rickettsia or virus was isolated. They had the misfortune of having secondary infections in both their inoculated and control animals. For this reason we do not feel

that this is a valid negative. The materials were obtained from only 3 patients early in the disease.

Table 2 summarizes the primary inoculations from our 6 patients to various animals. In any case where a primarily inoculated animal showed any abnormality whatsoever material was taken from him and passed through serial passages into other animals including the chick embryo.

TABLE 2.—RESULTS OF ANIMAL INOCULATIONS FROM 6 CASES.

Case No.	Day of illness.	Guinea pigs.	Mice.	Chick embryos.
		Number used, material and route of inoculation.	Number used, material and route of inoculation.	
1	10th	2: Blood: I.P.	2: Blood: I.P. 2: Saline gargle: I.N.	
6	5th	2: Blood: I.P.	2: Blood: I.P. 2: Saline gargle: I.N.	
7	5th	2: Saline gargle: I.P. 2: Saline gargle: I.N.	
8	2d	2: Blood: I.P.	2: Blood: I.P. 2: Saline gargle: I.N.	Yes; blood and saline gargle.
9	2d	2: Blood: I.P.	2: Blood: I.P. 2: Saline gargle: I.N.	Yes; blood and saline gargle.
10	3d	2: Blood: I.P.	2: Blood: I.P. 2: Serum: I.C.	

A variety of names has been applied to this clinical entity: "Acute Influenza Pneumonitis" (Bowen³); "Type A Virus Pneumonia" (Reimann¹⁴); "Acute Interstitial Pneumonia" (Smiley¹⁷); "Focal Disseminated Pneumonia" (Seadding¹⁶); "Atypical Bronchopneumonia" (Murray¹³); "Atypical Pneumonia" (Cass⁵); "Bronchopneumonia, Variety X" (Longcope¹⁰). The term pneumonia has always meant inflammation in the lung regardless of etiology. There seems, therefore, no reason to speak of these cases as pneumonitis. It would seem wise at this time to follow Longcope's lead and speak of this disease as bronchopneumonia of unknown etiology, Variety X, until the causative agent is established beyond question.

Summary. An outbreak of bronchopneumonia in a girls' school occurred between November 25, 1940, and January 7, 1941, affecting 13 of 90 students, an incidence of 14.4%. Previously reported outbreaks have been largely among males. The illness began, as a rule, abruptly with headache, mild sore throat and fever. This was shortly followed by a characteristic dry, harsh, non-productive cough. Abnormal lung findings were absent early, and even later in the disease were less than would be expected in patients having definite lung infiltration. Leukopenia or normal leukocyte counts were present and the sputum contained a mixed flora. Roentgen ray films of the chest usually showed an infiltration of moderate density beginning at the hilum and later extending in a fan-like fashion towards the periphery of the lung. This was usually limited to one lobe. The disease was mild in character and rarely accompanied by toxemia. Fever persisted for from 1 to 14 days. There were

no deaths. No virus or rickettsia were obtained by animal inoculations.

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CORRELATION BETWEEN CLINICAL AND IN VITRO REACTIONS OF GONOCOCCUS STRAINS TO SULFATHIAZOLE.

(A PRELIMINARY REPORT.)

By ALFRED COHN, M.D.,

ARTHUR STEER, M.D.,

AND

IRMA SEIJO, B.S.,

NEW YORK, N. Y.

(From the Bureau of Laboratories, Department of Health, City of New York.)

FELKE,¹ Levaditi and Vaisman,⁴ and Herrold² have reported the occurrence of gonococcus strains which were resistant to sulfanilamide. Westphal, Charles and Carpenter⁵ developed, experimentally, strains resistant to sulfapyridine.

The following *in vitro* bactericidal test, a modification of the technique developed by Keefer and his coworkers,³ demonstrated gonococcus strain reactions to sulfathiazole which corresponded to the results of chemotherapy in the patient.

Method. The test was carried out as follows: Citrated blood obtained from patients who had received 2 gm. of sulfathiazole 4 hours previous to the taking of the blood was divided into two parts, one of which was inactivated at 56° C. for 30 minutes. Various saline dilutions (10^{-1} , 10^{-2} , 10^{-3}) of a 24-hour growth of gonococci in 20% ascitic broth were added in 0.1 cc. amounts to tubes containing 0.5 cc. of the active or inactivated blood. The inoculated blood was incubated for 24 hours at 36° C. and 0.1 cc. from each tube was pipetted on to cooked blood filtrate ascitic fluid agar plates. These were incubated at 36° C. for 48 hours before being read.

Controls were set up by substituting 20% ascitic broth for the blood, and adding 4 mg. per 100 cc. of sulfathiazole.

Experiments were also made by adding p-aminobenzoic acid⁶ to the tubes containing sulfathiazole in blood or ascitic broth so that the final concentration of the acid was 5 mg. per 100 cc.

Active blood containing sulfathiazole did not give evidence of gonococcus strain differences. However, such differences of behavior were clearly demonstrated when inactivated blood was used. It was found that most strains obtained from patients who had responded to sulfathiazole did not grow in inactivated blood containing the drug, even with the higher concentrations of the organisms. On the other hand, strains obtained from patients who did not respond to therapy often showed growth with dilutions of 10^{-5} of the organisms (Table 1). This strain difference was not so evident when ascitic broth was used instead of inactivated blood.

TABLE 1.—EFFECT OF INACTIVATED HUMAN BLOOD CONTAINING SULFATHIAZOLE ON THE VIABILITY OF GONOCOCCUS STRAINS.

Dilutions of broth culture of gonococci:		10^{-1}		10^{-2}		10^{-3}		10^{-4}	
Strain.	No. of tests.	+	O.	+	O.	+	O.	+	O.
<i>A. Strain Susceptible to Sulfathiazole.</i>									
S1	37	15	22	1	36	1	36	1	36
S2	22	5	17	0	22	0	22	0	22
S3	12	4	8	0	12	0	12	0	12
S4	8	0	8	0	8	0	8	0	8
S5	6	6	0	1	5	0	6	0	6
S6	5	0	5	0	5	0	5	0	5
S7	4	0	4	0	4	0	4	0	4
S8	3	0	3	0	3	0	3	0	3
S18*	2	2	0	0	2	0	2	0	2
<i>B. Strains Resistant to Sulfathiazole.</i>									
R1	56	56	0	55	1	44	12		
R3	11	11	0	9	2	6	5		
R4	11	10	1	9	2	7	4		
R5	9	9	0	8	1	5	4		
R6	7	7	0	7	0	2	5		
R7	5	5	0	5	0	2	3		
R8	5	5	0	3	2	1	4		

+ = Growth. O = No growth.

* With 8 other susceptible strains, one test for each showed no growth in all 3 dilutions.

Comparison of the bactericidal power of blood containing sulfathiazole with the same blood containing p-aminobenzoic acid in addition, showed that susceptible strains were protected from the action of the sulfathiazole by the acid while resistant strains were either unaffected or made more susceptible to the action of the drug (Table 2).

Two strains, S7 and S8, obtained from patients who were apparently carriers, acted like susceptible strains. Each time the patients were given sulfathiazole, they appeared to respond in the typical manner, only to show a recurrence at a later date.

It was found that the behavior of a particular strain of organisms once isolated from the host, remained unchanged, in spite of the numerous passages on artificial media. However, it is known that some patients do not respond to the first course of treatment, but may respond to a second or third course. This makes one suspect

the existence of a host factor which was not demonstrated by the test.

TABLE 2.—EFFECT OF INACTIVATED HUMAN BLOOD CONTAINING SULFATHIAZOLE AND P-AMINO BENZOIC ACID ON THE VIABILITY OF GONOCOCCUS STRAINS.

Dilutions of broth culture of gonococci:								
Strain.	No. of tests.	10 ⁻¹		10 ⁻²		10 ⁻³		
		+	O.	+	O.	+	O.	
<i>A. Susceptible Strains.</i>								
S1	6	6	O	6	O	5	1	
S2	3	3	O	3	O	2	1	
S6	5	5	O	5	O	5	O	
<i>B. Resistant Strains.</i>								
R1	10	10	O	7	3	3	7	
R4	9	9	O	8	1	6	3	
R5	9	9	O	9	O	8	1	
R6	1	1	O	1	O	1	O	
R7	5	5	O	5	O	3	2	
+ = Growth. O = No growth.								

+ = Growth. O = No growth.

There was a lack of clinical and laboratory correlation for 2 strains of the 34 studied. One was a susceptible strain (S18), obtained from a patient resistant to sulfathiazole therapy. The other was a resistant strain (R5), obtained from a patient who responded to sulfathiazole treatment. It is suggested that the strain may undergo a change in the host from a resistant to a responsive character. Investigation along these lines will be continued.

Summary. A technique is described which gives evidence of a difference in behavior of various gonococcus strains to sulfathiazole *in vitro*. The strain variation corresponds markedly with the clinical reaction of the patient. Para-aminobenzoic acid inhibits the bactericidal effect of sulfathiazole on susceptible strains of gonococci.

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THE FORMOL-GEL TEST IN RHEUMATIC FEVER.

By J. SCOTT BUTTERWORTH, M.D.,

FRANK MELVILLE FELLOW IN CARDIOLOGY; NEW YORK POST-GRADUATE MEDICAL SCHOOL, COLUMBIA UNIVERSITY,
AND

CHARLES A. POINDEXTER, M.D.,

ASSOCIATE CLINICAL PROFESSOR OF MEDICINE, NEW YORK POST-GRADUATE MEDICAL SCHOOL, COLUMBIA UNIVERSITY,
NEW YORK, N. Y.

(From the Division of Cardiology, Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University.)

SINCE the formol-gel test was first described by Gaté and Papacostas⁵ in 1920, it has been recommended as a diagnostic aid in many diseases. The reaction was thought to occur only in the

serum of syphilitic patients but it has since been found to be present in a great variety of unrelated conditions.^{6,10,12}

Our attention was first drawn to the test by the report of Schultz and Rose⁹ in 1939. These authors compared the formol-gel test with the erythrocyte sedimentation rate (ESR) in cases of rheumatic fever and rheumatic heart disease as well as in an assorted group of "control" cases. They found that in patients with various febrile diseases excluding rheumatic fever there was a parallelism between the ESR and the formol-gel test and that a positive formol-gel test never occurred unless a certain degree of increased erythrocyte sedimentation existed. However, in children or adults with rheumatic carditis the test became positive when signs of active carditis appeared and the results were not necessarily parallel to the ESR.

They also noted occasional instances in which the formol-gel test remained positive after the ESR had returned to normal and suggested that this test might be a more sensitive index of persisting rheumatic infection. In cases of active rheumatic carditis with decompensation the formol-gel test was positive, whereas the ESR was within normal limits. These observations suggested to the authors that the formol-gel test might be a valuable additional aid in determining the presence of active carditis in patients known to be suffering from rheumatic fever.

Material and Methods. Three hundred and thirty-eight tests were performed on 208 patients. For the most part these patients were adolescents and adults, but a few children were included. The series consisted of a large number of patients with rheumatic valvular disease of varying degrees of activity. As controls, healthy individuals and patients with a variety of diseases seen on a general hospital ward service were included.

All bloods were taken by venipuncture, placed immediately in clean test tubes and allowed to stand until clot retraction had taken place. These were not necessarily fasting specimens. The tubes were then centrifuged and 1 cc. of serum was withdrawn and placed in a small test tube of 0.8 mm. bore. Two drops of a 40% formaldehyde solution were added to each tube. The tubes were then tightly stoppered and inverted until thorough mixing had occurred. The tubes were inspected at intervals of 24, 48 and 72 hours and the degree of gelation recorded. Early in the work the tubes were inspected at the end of 5-minute and 1-hour intervals, but this was soon discarded, since no additional information was gained. The degree of opacity was likewise found to be of little value and was abandoned.

The following criteria were adopted to denote the degree of gelation: 1. On inversion of the tube the serum showed a slight increase in viscosity when compared with normal serum. 2. On inversion of the tube the serum flowed very slowly when compared to normal. 3. On inversion of the tube there was no flow of serum but the surface had a jelly-like consistency. 4. On inversion of the tube a solid gel was present with no movement of the surface.

The ESR determinations were done by the Westergren method as modified by Berg.¹ For the purpose of this study all rates below 20 mm. per hour were considered to be normal or borderline, while all rates over 20 mm. per hour were considered definitely abnormal.

Results. Table 1 lists our results and indicates the relation of the ESR to the formol-gel test.

In 58 patients with clinically inactive rheumatic valvular disease of various degrees and with an ESR below 20 mm. per hour, the formol-gel test was invariably negative. In 9 additional cases where the ESR was between 20 mm. and 65 mm. per hour and in whom activity may have been present without clinical manifestations, the formol-gel test was negative in 7 and slightly positive in 2 cases.

TABLE 1.

Disease.	Total No. of cases.	ESR in mm. per hour.					Formol-Gel test.*			
		0- 10.	20- 39.	40- 59.	60- 79.	80+.	Neg. 59	Sl.*	Mod.*	Mark.*
Normals	59	59								
Rheumatic fever:										
Quiescent	58	58					58			
Questionable	9		7	1	1		7	2		
Active	16		1	4	4	7	3	1	3	9
Subacute bacterial en- docarditis	6				1	5	3	1		2
Coronary thrombosis . .	6	3	2	1			6			
Cirrhosis of liver . . .	4		2			2		1		3
Rheumatoid arthritis . .	14	1	5	3	2	3	7	2	2	3
Malignancy	5	2				3	5			
Miscellaneous:										
Acute and chronic in- fections	31	8	6	5	5	7	26	3	1	1
Totals	208	131	23	14	13	27	174	10	6	18

* Markedly positive tests include all those with 4+ gelation after 24 hours; moderately positive tests include those with 3+ gelation in 24 hours and 3+ and 4+ gelation in 72 hours; slightly positive tests include all those of less degree than 3+ gelation at the end of 72 hours.

Sixteen cases of active rheumatic fever in the hospital wards were studied during the course of the disease. Thirteen of these cases at one time or another gave a positive formol-gel reaction which in general paralleled the ESR, particularly when the ESR was high. In 1 patient, however, with an ESR of 90 mm. per hour and showing typical migratory arthritis, subcutaneous nodules and tachycardia, the formol-gel test was never positive. Another case was that of an 8-year-old boy with severe active rheumatic pericarditis and an ESR of 133 mm. per hour. The formol-gel test was negative until late in the course of the disease when the signs of active carditis had disappeared. The diagnosis of active rheumatic carditis is often extremely difficult even with the aid of modern laboratory techniques. The electrocardiogram may be of help, but interpretations must be made with caution.⁸

Six cases of coronary thrombosis were tested. The formol-gel test was invariably negative, although the ESR was above 20 mm. per hour in 3 of the cases.

Six cases of subacute bacterial endocarditis were followed over periods of many weeks. The diagnosis was definitely established in all cases and eventually all died. Two cases showed a positive formol-gel test, 3 were always negative and 1 was sometimes posi-

tive and sometimes negative. The ESR was markedly elevated in each case.

In studying liver and gall bladder disease it was found that the formol-gel test was usually positive in cases of cirrhosis, but not invariably so. One case of acute catarrhal jaundice and 2 cases of acute cholecystitis were negative.

In 14 cases of rheumatoid arthritis the ESR was over 20 mm. per hour in each case. Seven of the cases showed a formol-gel test positive in some degree and 7 were negative. One case of gout with an ESR of 103 mm. per hour was negative.

Weltmann¹¹ tests were performed with the ESR and the formol-gel test in 8 selected cases, but no correlation was found.

Discussion. All evidence to date^{3,4} points to the fact that the formol-gel test is a test for hyperglobulinemia and has no specificity in individual diseases. A recent paper by Biguria and Foster² proposed modifications of the test for the determination of globulin content of serum. Our results have likewise shown no specificity and we have been unable to corroborate many of Schultz and Rose's results. It is true that a positive formol-gel test rarely occurs with a normal sedimentation rate except in the presence of cardiac decompensation but on the other hand there is no correlation between a high ESR and the formol-gel test. Nor were we able to demonstrate that the formol-gel test was of value in determining the degree of carditis present. None of the cases of coronary occlusion with cardiac degenerative changes gave a positive test and 1 case of unquestionable rheumatic pancarditis gave negative results.

Schultz and Rose suggested that the test might be a more sensitive index of persisting rheumatic activity than the ESR. The formol-gel test may remain positive in cases of rheumatic fever after the ESR returns to normal ranges, but in our experience this alone is not an indication of persistent rheumatic activity that should keep the patient in bed. Our cases with a normal ESR but a persisting positive formol-gel test did well on gradually increasing activity, although this test often remained positive in some degree for long periods.

The formol-gel test has one advantage over the ESR in that the test does not have to be performed immediately. We have retested many sera after preserving them in the refrigerator for periods as long as 2 months and the results were essentially the same. This fact, however, does not compensate for the lack of sensitivity of the test.

Since this work was completed, a paper by Klein, Levinson and Stubik⁷ has appeared covering a study of the formol-gel test, the ESR and the Weltmann reaction in the rheumatic fever of childhood. Their results were entirely similar to ours in that they were unable to substantiate the claim that the formol-gel test was a measure of rheumatic carditis. In their experience the formol-gel

test was the least sensitive of the three procedures in determining the degree of activity in patients with rheumatic fever.

Summary and Conclusions. 1. The formol-gel test is essentially a test for hyperglobulinemia and has no correlation with the erythrocyte sedimentation rate.

2. It is of little or no value in the diagnosis of acute rheumatic fever with or without carditis.

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BOOK REVIEWS AND NOTICES

DOCTORS DON'T BELIEVE IT—WHY SHOULD YOU? Facts and Fallacies About Health with Practical Guide for the Layman. By AUGUST A. THOMEN, M.D., with Introductions by LOGAN CLENDENING, M.D., and The Right Honorable LORD HORDER, Physician in Ordinary to the King of England. Pp. 384. New York: Simon and Schuster, 1941. Price, \$2.50.

WRITTEN for laymen, this book will be welcomed and appreciated by all physicians because it so splendidly fulfills the promise of its subtitle. There are facts in a wide range of medical knowledge, wisely selected and well presented, interlarded with exposures of many fallacious beliefs current among the laity. The mode of presentation is ingenious and effective, taking the form of questions—254 of them—and their answers, ranging from a few words up to 30 pages. They are grouped under these chapter headings: Food, diet, and weight reduction; your daily life; major ailments; the venereal diseases; cancer; the common cold; allergy, asthma, and hay fever; minor ailments and remedies; mind and senses; birth, marriage, and death. The material is timely, accurate and interesting, so that the book should prove most popular and useful.

R. K.

OUTLINES OF INDUSTRIAL MEDICAL PRACTICE. By HOWARD E. COLLIER, M.D., CH.B., Formerly Reader in Industrial Hygiene and Medicine, University of Birmingham; Certifying Factory Surgeon, etc. Pp. 440. Baltimore: The Williams & Wilkins Company, 1941. Price, \$5.00.

THE problems of industrial hygiene and medicine are extensive, and a comprehensive discussion of the whole subject can hardly be presented within a single volume. The author has not attempted to do so. He has selected his material well and it is evident that it is presented from a background of considerable experience in the field of industrial medicine. While the subject is discussed from the British point of view, much of direct interest to American industrial physicians will be found. Extensive reference is made to American as well as British literature.

The subject matter is divided into five parts which are self-explanatory from their titles: Executive duties, advisory functions, industrial psychology, industrial medicine, industrial forensic medicine. The discussion of problems of industrial psychology is a welcome addition to a textbook on industrial medicine and its inclusion is indicative of the expansion of the duties of the industrial physician in the modern health program in industry. Of particular interest at the present time is the author's discussion of the influence upon the workers' efficiency and health of such factors as hours of labor, speed of work, overtime, night work, and so on. Experience during the last war showed clearly that the optimum rate of doing work could not safely be exceeded except for short periods. It is to be hoped that the mistakes of that period will not be repeated.

The discussion of industrial poisons is necessarily limited, the most important ones receiving the greatest consideration. The author would have done well to have limited it even more. A number of the less common poisons receive only brief mention. A mere listing of these substances, with suitable references, would have served as well and more space could have been given to the important toxic substances. The classification of agents causing occupational dermatoses and trade ulcers is excellent.

The final section on forensic medicine includes an excellent summary of the British laws which should serve as a basis for comparison with American practices.

The author has fulfilled in an excellent manner his purpose, which was to present an introduction to industrial medicine for those who contemplate entering this field.

T. H.

THE COMPLETE WEIGHT REDUCER. By C. J. GERLING. Pp. 246. New York: Harvest House, 1941. Price, \$3.00.

MUCH useful information for laymen on obesity: its causes and treatment, and especially on the many fads and quackeries that are perpetuated on the public in this field. The manner of presentation is novel. Instead of a systematic and consecutive covering of the subject, there are concise discussions, usually only a paragraph or two, on topics alphabetically arranged, to which the reader can easily refer when he wishes to look up a particular point. The book should prove helpful and instructive to the interested layman.

R. K.

A TEXT-BOOK OF PATHOLOGY. Edited by E. T. BELL, M.D., Professor of Pathology in the University of Minnesota, Minneapolis. Pp. 931; 431 illustrations and 2 colored plates. Fourth Edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, \$9.50.

EACH succeeding edition of this valuable textbook brings it nearer in size to the Big Three works on this subject, without loss of quality. Favorably comparing with them is the lower price of Bell's work, and the greater attention paid to predisposing factors in disease and to physical and chemical agents. There is a welcome increase in the emphasis on pathologic physiology, and a desirable tie-up with clinical medicine, without sacrifice of space devoted to the basic concepts on general pathology.

E. K.

THE INTERVERTEBRAL DISC. With Special Reference to Rupture of the Annulus Fibrosus with Herniation of the Nucleus Pulposus. By F. LEITH BRADFORD, M.D., Houston, Texas and R. GLEN SPURLING, M.D., Louisville, Ky. Pp. 158; 45 illustrations. Springfield, Ill.; Charles C Thomas, 1941. Price, \$4.00.

IN this monograph discussion of diseases and traumata of the intervertebral disc, special attention is given to the nucleus pulposus. The scope of the work is comprehensive and inclusive. Anatomy, physiology and pathology are adequately considered and clinical phases of diagnosis and treatment receive detailed study. Differential diagnosis is somewhat sketchy, and conditions producing the symptoms of herniated disc are not given a true percentage valuation.

The illustrations are excellent, the format and paper are up to the Thomas standard. This monograph is of distinct value and is a contribution worthy of study and frequent reference.

G. W.

TRAUMA AND DISEASE. Edited by LEOPOLD BRAHDY, B.S., M.D., Physician in Charge of Occupational Diseases and Injuries in the Office of The Corporation Counsel of the City of New York, etc., and SAMUEL KAHN, B.S., M.D., Medical Examiner in the Bureau of Workmen's Compensation of the Department of Labor, State of New York. Pp. 655; 13 illustrations. Second Edition. Philadelphia: Lea & Febiger, 1941. Price, \$7.50.

THIS second edition continues the high standard set by the first. To the list of well-known authors who have contributed chapters have been

added Dr. Edward N. Packard, with a chapter on tuberculosis, Dr. George Blumer, who has rewritten the chapter on pulmonary diseases, and Dr. Robert J. Joplin, who has materially added to the chapter on bone diseases. Throughout, additions have been made as knowledge has accumulated, and this is especially true in the chapter on the relation of trauma to heart disease, where recent experimental work is cited. There are a few new illustrations and, in all, about 40 new pages of text. The book remains as a very valuable possession. It should be of particular interest to physicians in compensation practice and to compensation referees and lawyers. The work differs from several other books on the same subject in that each section is written by a man who is a recognized authority in his field.

L. F.

PATHOLOGY FOR STUDENTS AND PRACTITIONERS OF DENTISTRY. By WILLIAM E. EHRLICH, M.D., Associate in Pathology, School of Medicine, University of Pennsylvania. Pp. 509; 234 illustrations. Philadelphia: Lea & Febiger, 1941. Price, \$5.50.

In a short period of time several new textbooks have appeared outlining courses of pathology for dental students. Ehrlich's book is not just another of these texts. In the present educational set-up it is as a rule, deemed unnecessary to acquaint dental students with the principles of pathology as taught to medical students. If one is of this opinion then it becomes a difficult task to select from the general subject matter such material as may be suited to adequately support the study of oral disease. The author has been successful in such an attempt.

Having taught pathology to both medical and dental students he is eminently qualified to make this endeavor and we think his results testify to this fact. His correlation of systemic and local conditions is definitely aimed at widening the mental horizon of the future practitioner of dentistry, who too often regards the mouth and the teeth as anatomic entities whose rôle in the somatic functional processes is an insignificant one. We therefore welcome this effort at correlation. Moreover, the author has integrated skillfully, where possible, the pictures of tissue changes and functional disturbances, a practice which is so essential to an understanding of disease.

The arrangement of the chapters is unusual for a textbook on pathology. Inflammation is discussed in the last chapter which places the subjects of pulpitis and parodontitis at the end of the book. Controversial topics such as parodontitis (14 pages with 13 illustrations) and caries (14 pages with 9 illustrations) might well receive more elaborate treatment in a next edition. The bibliography is definitely partial to the European literature. The literary aspect of the book could be improved upon. However, we feel that the dental student and the practitioner will be greatly benefited by reading and frequently consulting Ehrlich's book. It contains much information rarely embodied in textbooks of this kind, and we therefore recommend it warmly to the dental profession.

H. C.

BODY MECHANICS IN HEALTH AND DISEASE. By JOEL E. GOLDTHWAIT, M.D., F.A.C.S., LL.D., LLOYD T. BROWN, M.D., F.A.C.S., LORING T. SWAIN, M.D., and JOHN G. KUHN, M.D., F.A.C.S. With a Chapter on the Heart and Circulation as Related to Body Mechanics, by WILLIAM J. KERR, M.D., F.A.C.P. Pp. 316; 121 illustrations. Third Edition, completely revised and reset. Philadelphia: J. B. Lippincott Company, 1941. Price, \$5.00.

The keystone of the Boston School of Orthopaedics has long been the work of Goldthwait on posture and body mechanics. In the third edition

of this work the views of Goldthwait are presented and augmented by his pupils. The greater portion of the book is sound and of value. Some wishful thinking and loose statement has, however, crept into the work. Especially is this true as regards vascular disease. Certainly the proper critical attitude has not been applied to the relationship between skeletal structure and position and the development and treatment of visceral diseases.

G. W.

IMMUNITY AGAINST ANIMAL PARASITES. By JAMES T. CULBERTSON, Assistant Professor of Bacteriology, College of Physicians and Surgeons, Columbia University. Pp. 274; illustrated. New York: Columbia University Press, 1941. Price, \$3.50.

THE subject matter of this book is divided into three parts: 1, Natural Resistance and Acquired Immunity; 2, Immunity in Specific Diseases; and 3, Applied Immunology. Part I contains 7 chapters, the headings of which are: Natural Resistance, Age Resistance, Specifically Acquired Immunity, Requisite for Immune Response, Parasites Which Elicit Immunity, Mechanisms of Specific Immunity and Demonstration of Immunity. Part II is made up of the following 9 chapters: Amœbiases, Leishmaniasis, Trypanosomiasis, Malaria, Coccidiosis, Trematodiasis, Cestodiasis, Nematodiasis, and Response to Arthropods. Part III is composed of the following: Classification of Parasites, Vaccination Against Parasites, and Diagnosis of Parasitic Infection. A list of abbreviations of journal titles and an index complete the book. The text is illustrated by 4 plates, 3 charts and 2 tables.

To this Reviewer the chief value of the book is its extensive bibliography, which supplements that of Taliaferro's (1929) "The Immunology of Parasitic Infections." On the whole, one gets the impression of hurried preparation, inadequate digestion of data and of carelessness. The last may be illustrated by expressions such as "malaria-infected blood," "monkey malaria," "choice of hosts," "the balantidias" for species of balantidium, "Balantidia" written as a generic name, "somatic protozoans" for protozoa that are parasitic in tissue. Throughout the text results of experiments are cited without analytical consideration of their part in aiding a rational explanation of the interrelationships of host and parasite. There seems to have been no attempt to differentiate between truly pathogenic and non-pathogenic parasites or "normal" and "abnormal" parasitism in discussing immunologic responses. This Reviewer cannot agree that "examples of extreme maladjustment between host and parasite do not occur . . . in natural infections" (p. 14), that "age resistance has been demonstrated to" parasitic amœbæ or flagellates of the intestinal tract (p. 37), that "once a parasite has developed to a stage which can survive in the intestinal lumen . . . it is largely beyond the influence of the agencies . . . which perform the immune function" (p. 60), that "the depression of egg production by female worms in immune hosts may be explained by occlusion of the genital pore with precipitate" "(precipitated antibody)" (p. 72), that "most human beings are naturally resistant to infection with *Endamoeba histolytica*" (p. 92), or that eosinophile leukocytes, by collecting in the intestinal mucosa "form a definite barrier to penetration by the adult parasites" (*Trichinella spiralis*) (p. 192).

This Reviewer has no wish to belittle in any way the excellent studies that have been and are being made on the immunology of parasitic diseases. Certainly this phase of parasitology would not have attracted the attention of our best-equipped investigators had it not presented so many fascinating problems. It warrants better treatment than has been its lot this time.

H. R.

THE BAKER MEMORIAL, 1930-1939. A Study of the First Ten Years of a Unit for People of Moderate Means at the Massachusetts General Hospital. By HAVEN EMERSON, M.D. Pp. 75; 1 illustration. New York: The Commonwealth Fund, 1941.

This book is at once an accounting of 10 years of successful stewardship and an able appeal for other communities to develop adequate facilities for the care of our large group of citizens of moderate means. The following paragraphs from the volume capably describe its purpose and content:

"The Baker Memorial remains unique in hospital experience with its consistent coöperative pattern, by which the supporting community, the hospital administration, the medical and nursing staffs, and the patients share in obtaining bed care of superior quality for the sick at a cost which people of moderate means can pay."

"After a brief review of the chronological development of the idea of a self-supporting hospital for private patients of moderate means, from its first expression, through the stages of discussion, acceptance, construction, and operation, the significant facts as to use of the hospital during the ten-year period will be presented and the reaction of patients and physicians considered."

"The financial experience of the hospital will be described and its economic and social implications for possible application of similar principles for hospital care in other communities will be discussed."

B. B.

A BRIEF COURSE IN ORGANIC CHEMISTRY. A Combined Textbook and Laboratory Manual. By REYNOLD C. FUSON, Professor of Chemistry in the University of Illinois, RALPH CONNOR, Associate Professor of Chemistry in the University of Pennsylvania; CHARLES C. PRICE, Assistant Professor of Chemistry in the University of Illinois, and H. R. SNYDER, Assistant Professor of Chemistry in the University of Illinois. Pp. 248; 24 illustrations. New York: John Wiley & Sons, Inc., 1941. Price, \$2.50.

Although this excellent combined textbook and laboratory manual has been designed for students of pre-medicine or related fields, it may also be of value to certain physicians who desire to have at hand a concise reference book concerned with broad, fundamental concepts in organic chemistry. The material is clearly presented, and, although condensed, is quite up-to-date. The later chapters dealing with Coal-Tar and Natural Products constitute a convenient source of information pertaining to sulfonamides, vitamins, hormones, etc.

F. S.

SURGERY OF THE HEART. By E. S. J. KING, M.D., M. S., D.Sc. (Melb.), F.R.C.S. (Eng.), F.R.A.C.S., Major A.A.M.C., Honorary Surgeon to Outpatients, Royal Melbourne Hospital; Jacksonian Prizeman, Royal College of Surgeons; etc. Pp. 728; 268 illustrations and 4 color plates. Baltimore: The Williams & Wilkins Company, 1941. Price, \$13.50.

The title of this monograph is somewhat misleading. "What a Cardiac Surgeon Should Know" would more nearly describe the contents. The first third of the book is concerned with the anatomy, physiology and pathology of the heart. The second two-thirds are mainly descriptions of heart disease in the classical manner: history, etiology, pathology, symptoms and signs, treatment and prognosis of the various conditions. Only a few of the diseases of the heart are amenable to surgical therapy, but without doubt a surgeon venturing into this field should be familiar with all the conditions discussed.

The author has proved himself to be truly a doctor of medicine as well as a surgeon, and this book is to be commended as an example of the general information that the surgeon should possess rather than the purely technical information of the "operator."

I. R.

HYPOPARATHYROIDISM IN DENMARK. A Clinical Study. By AAGE LACHMANN. Pp. 269; illustrated. Copenhagen: Einar Munksgaard, 1941. Price, Dan. Cr. 12.

THIS is a summary of the clinical and metabolic findings in patients with postoperative and idiopathic hypoparathyroidism, with results of various treatments. It consists of studies on patients in several Danish hospitals and analysis of data in the literature of other countries.

I. Z.

THE FOOT AND ANKLE. Their Injuries, Diseases, Deformities and Disabilities with Special Application to Military Practice. By PHILIP LEWIN, M.D., F.A.C.S., Associate Professor of Bone and Joint Surgery, Northwestern University Medical School; Professor of Orthopedic Surgery, Post-Graduate Medical School of Cook County Hospital, etc. Pp. 665; 304 line drawings by HAROLD LAUFMAN, M.D. Second Edition. Philadelphia: Lea & Febiger, 1941. Price, \$9.00.

THIS book is well on the way to becoming a classic. The second edition is much superior to the first. Experience has shown what to eliminate and condense. Necessity has caused inclusion and elaboration of lesions peculiar to the soldier and war. In its present form this book is of great worth and can be unhesitatingly recommended as the best treatise upon the subject.

G. W.

THE MEDICAL CLINICS OF NORTH AMERICA (Vol. 25. No. 5, Boston Number). September, 1941. Philadelphia: W. B. Saunders Company, 1941.

THIS number features a symposium on methods of treatment in diabetes, pneumonia, pulmonary tuberculosis, common forms of heart disease, bacterial meningitis, migraine, epilepsy, exophthalmic goiter, peptic ulcer, gall bladder disease, nephritis and urinary tract infections. The issue also contains articles on infant feeding, the preventative aspects of military medicine, conditions simulating pulmonary tuberculosis and the clinical application of electro-encephalography.

The subjects are well presented, new methods as well as old being discussed, though some can scarcely be considered "specific." The majority of the articles discuss both diagnosis and therapy. The rôle of sulfonamide therapy in the various indicated diseases is properly evaluated in most instances, though the value of these drugs in subacute bacterial endocarditis is perhaps overrated. The article on diabetes contains valuable advice on its management in automobile drivers. In the section on the treatment of meningitis there is a great deal of repetition and, after ascribing a high incidence rate (first in some reported series) to tuberculous meningitis, the treatment of this disease is not discussed, perhaps because of the hopeless prognosis in this type. In the treatment of acute cholecystitis, the administration of only sodium chloride solution intravenously is recommended, though the value of glucose, in such cases is well recognized. In the discussion of the diagnosis of gall bladder disease, there is no reference to the examination of bile obtained by duodenal aspiration as a diagnostic procedure.

T. M.

WOUNDS AND FRACTURES. A Clinical Guide to Civil and Military Practice. By H. WINNETT ORR, M.D., F.A.S.C., Lincoln, Nebraska; Chief Surgeon, Nebraska Orthopedic Hospital. Pp. 227; 137 illustrations. Springfield, Ill.: Charles C Thomas, 1941. Price, \$5.00.

This book is in reality a monograph on Dr. Orr's method of treating fractures rather than the clinical guide that the title indicates. There is no question as to the brilliant results of the Orr methods of treatment in many cases, but it would be a mistake not to emphasize the fact that many fractures can be treated successfully without the use of pin fixation. In fact, it is doubtful whether the widespread use of pins should be encouraged.

The Reviewer also believes that infection in compound fractures may in part at least be combated by the use of sulfonamide therapy, but the use of this drug has not been mentioned by Doctor Orr. Does it not deserve a trial at his hands?

Aside from these two criticisms this volume deserves only praise for its exposition of this important method of treatment which has done so much to reduce mortality and morbidity in patients with compound fractures.

I. R.

SULFANILAMIDE AND RELATED COMPOUNDS IN GENERAL PRACTICE. By WESLEY W. SPINK, M.D., Associate Professor of Medicine, University of Minnesota Medical School. Pp. 256. Chicago: The Year Book Publishers, Inc., 1941. Price, \$3.00.

This is the fourth book on sulfonamide chemotherapy which has come to the Reviewer's attention in as many years, indicating the tremendous interest in the subject as well as the rapid advances which have been and are being made. Second editions or new ones will no doubt be needed in the near future.

The present volume is remarkably down to date, with the latest reference dated July, 1941. The subject matter is dealt with in an orderly manner beginning with the historical development and general principles of therapy. This is followed by a discussion of the three principally used compounds, sulfanilamide, sulfapyridine and sulfathiazole, describing for each in detail the dose and methods of administration, treatment of especially important infections, contraindications and so forth. Several chapters are devoted to disease complexes such as pneumonia, meningitis, urinary tract infection, and to chemotherapy in dermatologic, surgical, and dental fields. There are good chapters on chemoprophylaxis and toxic manifestations. The final two chapters discuss the available knowledge on the two most recently introduced compounds, sulfaguanidine and sulfadiazine.

The book is of convenient size and is written in a simple, clear, concise manner. It is remarkably free from typographic or other errors. Numerous interspersed case reports with charts illustrate important points in therapy. The bibliography is well arranged, adequate, and contains over 400 selected references. The index is complete.

The book has a justifiable enthusiastic tone but is tempered with the right amount of conservatism to make it a valuable one for the profession.

H. R.

A MANUAL OF THE TREATMENT OF FRACTURES. By JOHN A. CALDWELL, M.D., Professor of Clinical Surgery, College of Medicine, University of Cincinnati; Director of the Fracture Service, Cincinnati General Hospital, Cincinnati. Pp. 150; 76 illustrations. Springfield, Ill.: Charles C Thomas, 1941. Price, \$3.50.

On the jacket of this manual is the statement "A Plain and Simple Text;" to this might be added "Written with clarity, conciseness and

originality." Doctor Caldwell has emphasized principles of treatment, has shown standard procedures and has provided a guide to the literature so that any student or house officer can act in an emergency if he is familiar with this manual; but he will also be aware of the fact that more detailed instructions are available and that it will be of interest and benefit to him to go to the source for them.

This book is heartily recommended to any one interested in the treatment of fractures.

I. R.

LECTURES ON WAR NEUROSES. By T. A. Ross, M.D., F.R.C.P. Pp. 116. Baltimore: The Williams & Wilkins Company, 1941. Price, \$2.00.

A VERY colloquial, simple and short description of neuroses intended for general practitioners in civilian life and medical officers in the army.

It is very loosely knit together with many illustrative cases. The author insists on the need for prompt psychotherapy by whatever medical officers are near in the earliest hours of a war neurosis, and he describes the surprisingly good results from crude emergency measures. He advises that long-standing cases be handled only by psychiatrists.

E. B.

IMMUNIZATION TO TYPHOID FEVER. Results obtained in the prevention of typhoid fever in the United States Army, United States Navy, and Civilian Conservation Corps, by the use of vaccines: influence of antigenic structure and other biological characters of *E. typhosa* on the production of protective antibodies in the blood of immunized individuals: increases in protective antibodies in the blood following the use of a single small dose of vaccine for reimmunization purposes as compared with the use of three doses.

From the Research Laboratories of the Army Medical School, Washington, D. C. Investigations carried out under the general supervision of: COL. J. F. SILER, M. C., U. S. A.; LT. COL. GEORGE C. DUNHAM, M. C., U. S. A.; MAJ. DON LONGFELLOW, M. C., U. S. A.; LIEUT. G. F. LUFPOLD, San. Corps Res., U. S. A. Special investigations carried out and coöperative assistance rendered by the following members of the staff of the Medical Department Professional Service Schools, Army Medical Center, Washington, D. C.: MAJ. H. R. LIVESAY, CAPT. DON LONGFELLOW, CAPT. C. P. CANBY, CAPT. F. B. WAKEMAN, CAPT. F. E. COUNCIL, MAJ. F. H. K. REYNOLDS, LT. COL. A. P. HITCHENS, CAPT. WILLIAM S. STONE, LT. COL. W. D. FLEMING, CAPT. J. R. WOOD, CAPT. J. H. McNINCH, LT. COL. R. L. HOLT, CAPT. A. R. DREISBACH, and LT. COL. S. D. AVERY. (The Am. J. Hyg. Supported by the De Lamar Fund of The Johns Hopkins University. Pp. 276; illustrated. Monogr. Ser., No. 17, Sept., 1941.) Baltimore: The Johns Hopkins Press, 1941. Price, \$2.50.

A COMPILATION of the extensive investigations into the antigenic and immunizing properties of *E. typhosa* during the period of 1934-1940 is most timely. Although many phases of the experimental work were published elsewhere from time to time, this report presents the work in more detail. A historical review of the use of typhoid vaccine in the Army, Navy, and Civilian Conservation Corps is included. Detailed descriptions are given of the experimental investigations on the antigenic characteristics of strains of *E. typhosa*, on the ability of the various vaccines to bring about the production of protective antibodies, the duration of immunity subsequent to immunization with typhoid vaccine and the matter of revaccination.

Briefly the findings are that the strain of *E. typhosa* used in the production of vaccine should be one of high virulence, preferably it should have been freshly isolated from a human being, and also preferably, the colonies resulting from growth on agar should be of the "smooth" type. For initial immunization the standard method of three doses (1st dose 0.5 cc., 2d and 3d doses 1.0 cc. for adults) administered at intervals of 1 week should be followed (content of vaccine 1000 million *E. typhosa* per cc.). For reimmunization a single dose of a virulent type vaccine will result in adequate stimulation of antibody production. The single dose for reimmunization may be 0.5 cc. subcutaneously or 0.1 cc. intracutaneously, the latter method is to be preferred. Reimmunization should be carried out ordinarily between 2 and 3 years subsequent to initial immunization and this reimmunization should be repeated at least once at the end of another 2 to 3 years. H. M.

NEW BOOKS.

- Abdominal Surgery of Infancy and Childhood.* By WILLIAM E. LADD, M.D., F.A.C.S., William E. Ladd Professor of Child Surgery at Harvard Medical School; Chief of Surgical Service, The Children's Hospital, Boston, and ROBERT E. GROSS, M.D., Associate in Surgery, the Harvard Medical School; Associate Visiting Surgeon, The Children's Hospital; Associate in Surgery, The Peter Bent Brigham Hospital, Boston. Pp. 455; 268 illustrations. Philadelphia: W. B. Saunders Company, 1941. Price, \$10.00.
- Treatment of the Patient Past Fifty.* By ERNST P. BOAS, M.D., Associate Physician, Mount Sinai Hospital, New York City; Chairman, Committee on Chronic Illness, Welfare Council of New York City; Assistant Clinical Professor of Medicine, Columbia University. Pp. 324; 19 illustrations. Chicago: The Year Book Publishers, Inc., 1941. Price, \$4.00.
- The March of Medicine.* New York Academy of Medicine Lectures to the Laity, 1941. Pp. 154; 4 illustrations. New York: Columbia University Press, 1941. Price, \$2.00.
- The New International Clinics, Vol. IV, New Series 4, December, 1941.* Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, with 17 Collaborators. Pp. 314; illustrated. Philadelphia: J. B. Lippincott Company, 1941.
- In addition to 12 miscellaneous "clinics" from the University of Minnesota, and a 10-page progress review of The Surgery of Modern War, by Calvin M. Smythe, Jr., this number contains 11 "original contributions" from various sources on various subjects of greater and lesser importance and merit.
- The 1941 Year Book of Pathology and Immunology.* Pathology, edited by HOWARD T. KARSNER, M.D., Professor of Pathology, Director of the Institute of Pathology, Western Reserve University, Cleveland. Immunology, edited by SANFORD B. HOOKER, A.M., M.D., Professor of Immunology, Boston University School of Medicine; Immunologist, Massachusetts Memorial Hospitals. Pp. 623; 136 illustrations. Chicago: The Year Book Publishers, 1941. Price, \$3.00.
- Hérédité Mendélienne et Analyse Combinatoire.* By E.-L. ROULET. Pp. 193. Geneva: Georg et Cie, 1941. Price, Sw. Fr. 12.
- Allergy in Clinical Practice.* By Staff-Members of the Cleveland Clinic. Under the direction of RUSSELL L. HADEN, M.D., F.A.C.P., Chief of the Medical Division. Edited by J. WARRICK THOMAS, M.D., F.A.C.P., Chief of the Section on Allergy. Pp. 354; 92 illustrations (some in color). Philadelphia: J. B. Lippincott Company, 1941. Price, \$5.00.

Behind the Mask of Medicine. By MILES ATKINSON. Pp. 348. New York: Charles Scribner's Sons, 1941. Price, \$3.00.

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Language in Action. A Guide to Accurate Thinking. By S. I. HAYAKAWA, Assistant Professor of English, Illinois Institute of Technology. Pp. 245. New York: Harcourt, Brace & Co., 1941. Price, \$2.00.

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NEW EDITIONS.

Diseases of the Nervous System. Described for Practitioners and Students. By F. M. R. WALSH, O.B.E., M.D., D.Sc., F.R.C.P. (LOND.), Hon. D.Sc., National University Ireland, Physician in Charge of the Neurological Department, University College Hospital, London; Physician to the National Hospital for Nervous Diseases, Queen Square; Neurologist to the Hospital for Tropical Diseases, London, and the Seamen's Hospital, Greenwich. Pp. 325; 32 illustrations. Second Edition. Baltimore: The Williams & Wilkins Company, 1941. Price, \$4.50.

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PROGRESS OF MEDICAL SCIENCE SURGERY.

UNDER THE CHARGE OF
I. S. RAYDIN, B.S., M.D.,
HARRISON PROFESSOR OF SURGERY, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA, PA.,

AND
C. G. JOHNSTON, M.S., M.D.,
PROFESSOR OF SURGERY, WAYNE UNIVERSITY,
DETROIT, MICH.

CUTANEOUS BURNS.

SEVERAL excellent papers summarizing the recent work on burns have been published during the last few years, and it is not the purpose of this article to add another to that list. Rather, we will try to present a critical analysis of the status of the research and treatment of burns, no attempt being made to refer individually to all of the investigations which have contributed to the present concepts.

The cause of death after severe burns has long been the subject of much study and speculation. Many theories have been presented and disproved, many local applicants have been advocated and abandoned, and many tables of mortality statistics have been published—however, actual advancement in this study has been slow. It can be said that at present we do not yet know the best method of treating these injuries.

One difficulty arises from the great variation in reaction shown by individual patients. The more important variables which cause these differences are: *a*, the extent of the body surface involved; *b*, the depth of skin involvement; *c*, the particular region of the body affected; *d*, the different effects produced by the numerous etiologic agents; *e*, the age, sex, occupation and individual tolerance of the patient; *f*, the inhalation of flames, fumes or smoke at the time of injury; and *g*, the occurrence of various complications such as pneumonia, Curling's ulcer, and so on. Because of these variables mortality statistics are difficult to evaluate, and for this reason the current trend of clinical study has been toward a more thorough investigation of individual patients.

Stages of Reaction. Any discussion of the etiology of the clinical manifestations presented during the course of a burn is complicated by the differences in terminology and the classical division of the various

stages following the inception of the burn. For the sake of clarity Wilson's^{39a} classification of the stages of burn will be used in the following discussion, not because it is the more accurate or more desirable but because it may be more easily moulded to conform with the ideas of other investigators. Wilson lists the following stages: 1, initial shock; 2, secondary shock; 3, acute toxemia; 4, septic toxemia; 5, healing; 6, death in any of the above stages.

1. *Initial or Primary Shock.* This condition, which arises almost immediately after injury, is characterized by low blood pressure and has been considered to be due to vasomotor changes. It is probably produced by pain and fright since Underhill, Kapsinow, and Fisk³⁷ have demonstrated that it is not present when animals are burned under the influence of an anesthetic agent. Primary shock can usually be controlled in part by early adequate doses of morphine with supportive therapy, and care should be taken that the patient is past this stage before extensive local treatment of the burned area is started. Failure to realize this may lead to prolongation and intensification of the initial period of shock.

2. *Secondary Shock.* Underhill and his coworkers³⁶ as well as Robertson and Boyd^{29a,b} regarded secondary shock and acute toxemia as belonging to the same stage; however, in the light of recent investigation less confusion will result if these two stages are kept separate and the second stage of burns (secondary shock) referred to as the "period of hemoconcentration."

Cumin¹¹ in 1823 was the first to note a thickening of the blood after severe burns as he stated that bleeding was difficult because the blood was "sizy." Underhill, Carrington, Kapsinow, and Pack,³⁶ 100 years later, demonstrated a marked hemoconcentration in patients with severe burns. Experimental work by Underhill, Kapsinow, and Fisk³⁷ demonstrated in animals that the burning of one-sixth of the body surface caused a loss of 70% of the total blood volume into the burned area, and analysis of this fluid showed it to be similar to blood plasma. Experiments by Blalock,^{8a} Beard and Blalock,⁴ Harkins,^{17a,b} and others have confirmed this concept. The physiologic mechanism has been shown to be an increased capillary permeability in the burned area with a resultant rapid loss of plasma into this area occurring for the most part during the first 24 hours after injury. More recent studies demonstrate that a portion of the loss in plasma volume is from the surface of the burned area.

The clinical picture of this condition is one of hypotension, circulatory failure, and in severe cases, death. In fact the highest mortality occurs during this period. Hemoconcentration is easier to prevent than relieve. Parenteral fluid, especially plasma, should be started early since hemoconcentration increases most rapidly during the first 6 hours after injury. Weiner, Rowlette, and Elman³⁸ have emphasized the fact that large doses of parenteral saline are to be avoided since this frequently lowers the serum protein to an edema level, and the administration of large amounts of neutral sodium salts intensifies the edema at any given level of the serum protein. Wilson^{39b} also warned against large volumes of saline and glucose, and stated that he found gum acacia valuable in controlling hemoconcentration without lowering the level of the plasma protein. Since hepatic injury is often associated with an extensive burn this procedure is, we believe, attended with

some danger. The value of plasma administration has also been stressed by McClure,²⁵ by Elkinton, Wolff, and Lee,¹⁴ by Tenery³⁵ and Black.⁶ Ideally, the plasma lost into the burned area should be replaced volume for volume with plasma, but this is neither practical nor always necessary. We have found that most cases with 30% to 40% of the body affected with a first and second degree burn will do quite well when given 1000 to 3000 cc. of plasma plus not more than 1500 cc. of a 5% glucose solution in saline during the first 24 hours, if the oral intake of fluid can be kept up so that the urinary output is from 800 to 1000 cc. After this initial period, therapy should be dictated by following the hematocrit, plasma protein, and plasma chloride concentrations. The plasma replacement is best done slowly, for the administration of large amounts of plasma in a short time increases the loss of protein from the vessels.

3. *Acute Toxemia.* As no toxemia has been definitely demonstrated, it would perhaps be more accurate to refer to this as the "toxic stage of burns." Tissue toxins, bacterial toxins, and hemoconcentration have all been suggested as the etiologic factor in this stage. With adequate therapy, primary shock, hemoconcentration, and infection can be prevented or controlled—yet, the patient may still develop, usually 48 to 72 hours after the burn, a syndrome characterized by lowered blood pressure, tachycardia, hyperpyrexia, malaise, increasing lassitude, delirium, coma, circulatory failure, and, in some cases, death. This has led many investigators to further search for a toxic agent.

It is the etiology of this clinical picture which has long been the center of burn investigation. Excellent reviews of this problem have been published by Harkins,^{17c} Blalock,^{8b} and Gunn and Hillsman.¹⁶ Underhill believed that hemoconcentration accounted for the clinical picture seen in this stage, and Aldrich^{1a} feels that the absorption of bacterial toxins is the most important factor; however, as pointed out above, this syndrome may develop in the absence of hemoconcentration and infection. It has been noted when plasma replacement was sufficient to prevent hemoconcentration and hypotension had not taken place.

Much evidence has been presented to show the existence of a toxin formed in the burned area. Much of the older investigation along this line has been refuted; however, the work of Wilson, and of Rosenthal, has yet to be confirmed or condemned. Wilson, Jeffrey, Roxburgh, and Stewart¹⁰ in 1937, using rabbits, found that the edema fluid gradually became toxic, the potency being greatest after 48 hours after burning. This they attributed to autolysis of the injured tissue since culture indicated that bacteria played no rôle in this reaction. This late formation of a toxic material may explain why some previous investigators had found a toxin and others had not. Wilson,^{39b} however, stated that the existence of such a toxin has not yet been definitely proved. Also in 1937 Rosenthal^{31a, b} reported experiments in which he had found in the blood of burned animals a histaminoid substance which caused contraction of the virgin guinea pig uterus. This substance and histamine were both neutralized by the sera from experimental animals and humans in the healing stage of burns. Even normal sera neutralized these substances to a slight extent.

The work of Underhill, Kapsinow, and Fisk³⁷ indicated very little or no absorption of certain dyes and strychnine from the burned area

during the first 24 hours after injury; however, this need not indicate the lack of the later absorption of a toxin since this material is apparently not of great potency until about 48 hours after burning. The toxic stage usually does not appear until sometime after the first 24 to 48 hour period. Mason, Paxton, and Shoemaker²⁴ found that certain substances of low molecular weight such as sodium iodide, are quickly absorbed from the burned area in the first 24 hours, and Hooker and Lam¹⁸ have demonstrated the same result with sulfanilamide. The toxin may have a higher molecular weight and absorption may then be similar to the materials used in Underhill's experiments.

Recent blood electrolyte studies in burns have been of some interest. As early as 1926 Davidson^{13b} reported a lowering of the serum chlorides and evidence of a chloride retention which he suggested may lie in the tissues. Wilson and Stewart⁴¹ found a marked decrease in the serum sodium level which generally followed the severity of the patient's condition; the administration of desoxycorticosterone acetate was followed by elevation of the plasma sodium and with clinical improvement in the patients. They also noted some increase in the serum potassium level following severe burns but made little comment on this finding. Scudder³³ reported a study of plasma potassium levels on 6 patients following the Hindenburg disaster in whom he found elevation of plasma and whole blood potassium; he employed adrenal cortical hormone in the therapy of these cases with apparent success. Kceley, Gibson, and Pijoan,²⁰ however, found no elevation of serum potassium in dogs which were burned. Black⁶ has reported the finding of slight increases in chloride and potassium concentrations with lowering of the bicarbonate and sodium. Tenery³⁵ has studied the blood electrolytes in 8 severely burned patients, 3 of whom died. In these cases the plasma potassium rose slightly, the plasma chloride gradually fell, and the plasma sodium decreased markedly in spite of parenteral saline. The plasma potassium did not reach a toxic level, and the changes in the sodium level did not follow the clinical course. Since 6 of these patients showed evidence of the toxic stage, it was concluded that changes in blood electrolytes are not responsible for the toxic stage, though they must be considered in the general therapy of the patient. Harkins^{17c} and Tenery emphasized the fact that determinations of whole blood electrolytes in cases of severe burn are of little aid since these values will vary with changes in the hematocrit because of the difference between plasma and cellular concentrations. Lam²¹ has recently presented an excellent review of the literature on the blood chemical changes found in burns.

4. *Septic Toxemia.* This stage is generally admitted to be due to bacterial infection of the burned area, frequently with hemolytic streptococci; it is thought to begin when the temperature curve starts a septic swing, though Aldrich^{1a} believes that it starts much earlier. In the past, infection of the burned area was the common and expected occurrence, but at present is becoming less frequent.

This brings us to one of the most controversial subjects in the study of burns, namely, the treatment of the burned area.

Local Treatment. Almost everything in and out of the pharmacopeia has been used in the local treatment of burns. Because of the many variations presented by each individual case, the evaluation of these

agents is most difficult. Mortality statistics are even less reliable than data obtained from a study of the systemic changes.

The methods of local treatment in use today can be divided into four main types: 1, eschars; 2, wet dressing or submersion; 3, dressings with various agents which do not form eschars; 4, immediate skin grafting of the third degree burns.

1. *Eschars*. Certainly the introduction of tannic acid by Davidson^{13a} in 1925 was the greatest single advance in the treatment of burns, but this method has been greatly misused in that many have applied tannic acid to every burn regardless of the extent, depth, or location of the lesion. One has only to apply an eschar to the face on a single case of burn to learn that this can cause almost unbearable pain with every slight movement of the facial muscles. After the first 2 or 3 days, following injury the patient becomes truly "The Man in the Iron Mask." Likewise an eschar applied around the anus is apt to become infected and require removal. This is not a condemnation of the eschar treatment of burns. At present it is the most convenient method of handling a large body burn; however, any eschar has the disadvantage of not being the most applicable method for permitting early skin grafting.

Tannic acid alone has several disadvantages, the more important of which are: 1, the coagulum is brittle and tends to crack over areas subjected to bending, thus allowing bacteria to enter beneath the coat; 2, the eschar is quite stiff and tends to pull away and curl in at the edges and thus allows infection to enter; 3, the eschar is dense and fluid-proof so that underlying infection is at times masked; 4, several hours and many applications are required to form the coagulum.

With these disadvantages in mind and in an effort to eliminate infection, Aldrich presented the gentian violet^{1a} and later the triple-dye^{1b} treatments. This method eliminates all except the fourth disadvantage of tannic acid. Bettman⁵ advocated the use of tannic acid plus silver nitrate as this forms an immediate eschar which is, if properly and promptly applied, more pliable than when tannic acid is used alone. Branch⁹ then recommended the use of gentian violet with silver nitrate which makes a more pliable coagulum than that advocated by Bettman. Other eschar-forming agents advocated in the past are ferric chloride, horse serum, and picric acid. This latter is an excellent agent except for the disadvantage that too many individuals are sensitive to the drug.

The more recent addition to the list of eschar-forming agents is sulfadiazine in triethanolamine²⁸ which is said to produce a transparent, pliable eschar with the high antiseptic value of the sulphonamides. This treatment offers some promise, although it has the great disadvantage of requiring frequent applications over a long period before an eschar is obtained. Pickerell states that preliminary cleaning with soap and water is unnecessary before application of the solution, but this might prove to be unwise. This method has not been subjected to the wide application as have other agents and needs further study before general adoption.

2. *Wet Dressings*. In 1858 Passavant²⁵ introduced the continuous submersion treatment; he advocated the use of a tub of water to be changed 3 times daily. Blair, Brown, and Hamm⁷ in 1932 recommended the use of a daily tub bath of hypertonic saline, physiologic saline, or water. Lavender²² advised daily submersion in dilute green

soap solution with wet dressings of Burrow's solution during the intervals. The use of such baths continuously for the first few days after burning is valuable but has the disadvantage of requiring special equipment if many cases are to be handled. Darrow¹² has suggested that continuous or frequent bathing in hypotonic solutions may deplete the body of sodium chloride as the raw surface permits diffusion into the water. Salt solution should be used to obviate this difficulty. Wet dressings with physiologic saline solution are especially useful on hand and face burns and on burns that will require early grafting; however, this procedure requires added nursing care. Saline compresses are of undoubted value in the treatment of infected burns.

Bunyan^{10a,b} has made use of coated silk envelopes which are sealed around the upper portion of burned extremities; and irrigation with electrolytic sodium hypochlorite solution is carried out 3 times daily through openings into the envelope. This treatment allows free movement of the hands and feet and makes possible frequent inspection without the painful procedure of removing dressings. Bunyan has also devised coated silk coverings for treatment of other portions of the body. Hudson,¹⁹ Hannay¹⁶ and Pearson, Lewis and Niven²⁷ have all reported excellent results by the use of the envelope on burns of the extremities. The method could be used without the hypochlorite solution by substituting physiologic saline solution, with or without sulfanilamide.

3. *Dressings With Agents Which Do Not Form Eschars.* In 1914 Barthe de Sandfort³ introduced the paraffin wax treatment and this was in vogue until the introduction of tannic acid. Recently, there has been a trend to return to "greasy" applications. This has come about through the knowledge that the most virulent infections occur after the initial dressing and can be prevented if care is taken to prevent subsequent contamination. A definite advantage of this type of dressing is that it can be easily removed for early skin grafting of third degree burns. The essential technique of this method consists of covering the wound with an ointment, gauze, and protective dressing after making the wound surgically clean by washing with soap and water; the inner layer of gauze should then be left in place 7 to 14 days unless evidence of infection appears.

After a thorough cleaning of burns of the hand, Allen² uses plain vaseline gauze with a voluminous gauze pressure dressings and splints. MacCollum²³ emphasized the point that an eschar on burns completely encircling the fingers may impair circulation since it does not allow for swelling of the fingers. For this reason he recommended an ointment gauze dressing especially for this type of burn. Steel²⁴ and others have advised cod-liver oil dressings because of the supposed vitamin stimulation of epithelization. It is still questionable whether this does any good.

The use of sulfadiazine in triethanolamine covered after the first application with sulfadiazine ointment gauze²⁵ may offer a satisfactory method of treatment. Robson and Wallace³⁰ have recommended the use of glycerin-sulfonamide-kaolin paste. Pearson, Lewis, and Niven²⁷ report excellent results on face burns by the use of sulfanilamide powder covered with tulle gras.

After preliminary cleaning of infected burns of the extremities Roulston³² has covered the involved area with vaseline gauze and

enclosed the extremity in a plaster mold; he reports excellent healing, freedom from pain, subsidence of infection, and no added limitation of joint motion when the plaster is removed.

4. *Immediate Skin Grafting.* This procedure has a definite place in the treatment of small third degree burns as it will give the most rapid and best cosmetic result with a minimum of contracture. However, it is not always possible to know immediately which burns extend deeper than the hair follicle and sebaceous glands. It inflicts additional trauma in the extensively burned patient who is shocked and may soon enter the toxic stage and therefore should be reserved for those patients with small burned areas who are in excellent shape.

5. *The ideal local treatment* of burns should fulfill all of the following criteria:

1. Bacterial contaminants should be removed, destroyed, or their growth inhibited.
2. Subsequent bacterial contamination must be prevented.
3. The treatment should be carried out with a single, non-shocking procedure so that disturbance of the patient will be minimal while the systemic reaction is most severe.
4. The material applied to the burned area should not damage the living cells remaining, nor should it be toxic if absorbed in the quantity necessary to cover any given burn.
5. The burned area should be protected against trauma from brushing the bedclothes, and so on.
6. The covering should not mask underlying infection.
7. The covering should be easily removed so that early grafting can be carried out in the more extensive burns.
8. The covering should require a minimum of attention and should facilitate rather than hinder nursing care.

From the above one can see that there is still no ideal treatment which can be applied to all burns. Each case must be considered separately as an individual problem and one's armamentarium should include several types of treatment. It is important that cleaning the area with soap and water and débridement of loose tissues should be carried out in all cases. This procedure can be done on most patients with the aid of narcotics alone, although occasionally general anesthesia may be required.

R. MAYO TENERY, M.D.

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OPHTHALMOLOGY.

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.,

AND

H. P. WAGENER, M.D.

ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

OCULAR LESIONS IN THE SARCOIDOSIS OF BOECK.

It is assumed commonly that the various forms of involvement of the uveal tract, iritis, iridocyclitis, uveitis, choroiditis, are local manifestations of some systemic disease. The determination of the nature of the responsible systemic disease in the individual case frequently is quite difficult and taxes the diagnostic powers of both ophthalmologist and internist. Certain local features of the ocular disease may arouse the suspicion of a specific etiology. Thus, most cases of iridocyclitis which present nodules in the iris are suspected of being tuberculous. However, all cases of tuberculous iritis do not present nodules in the iris and all nodules in the iris are not tuberculous in origin. Therefore, to reduce as far as possible the number of cases of uveal disease in which the etiology is not determined, it is necessary for the ophthalmologist and the consulting internist to be familiar with the rarer as well as with the more common systemic causes of involvement of the uveal tract. For this reason, it seems worth while to call attention to the ocular manifestations of the systemic distribution of sarcoidosis which too frequently is thought of as a disease essentially of the skin.

Longcope and Pierson¹¹ stated that the lesions of sarcoïdosis are described in the literature under a great variety of names, such as "Inpus pernio" (Besnier), "sarcoid" (Boeck), "benignes miliar lupoid" (Boeck), "Boeck's sarcoid," "benign lymphogranulomatosis" (Schau-mann), "ostitis tuberculosa multiplex cystoides" (Jüngling), "maladie de Besnier-Boeck," and "Hutchinson-Boeck's disease." The most characteristic features of the disease as listed by Longcope and Pierson are, in the skin, firm red, violaceous, or brownish swellings usually well demarcated from the surrounding skin; in the lungs, roentgenographi-cally, enlarged peribronchial lymph nodes, increased hilar shadows, a marbled reticulated appearance of the lungs resembling miliary tuber-culosis or pneumoconiosis, the infiltration extending, however, from the roots of the lungs toward the bases rather than toward the upper lobes and apices; in the bones, roentgenographically, areas of rarefaction and reticulation distributed through the medulla of the phalanges of the hands and feet, sometimes with irregular enlargement and distortion of the bones but without involvement of the periosteum or joints, these changes being expressed clinically in some cases by irregular enlarge-ment of the fingers, dorsal flexion of the last phalanx and subcutaneous nodules around the interphalangeal joints; and in the eyes, iritis or iridocyclitis and nodules in the conjunctiva. Practically any organ or tissue of the body may be involved, so that generalized enlargement of the lymph glands and of the salivary and lacrimal glands may be seen, the spleen and liver may be enlarged, and the mucous membranes of the nose, nasopharynx and larynx may be involved. In essence, the disease seems to be, as summarized by Longcope and Pierson, a chronic infectious granuloma, insidious in onset, persisting often for years, sometimes spreading slowly from one organ or tissue to another, fre-quently relapsing, seldom producing serious constitutional symptoms, resistant to treatment but at times healing spontaneously. In King's⁹ opinion, "Boeck's sarcoid is a generalized granulomatous disease involv-ing primarily the lymph nodes, the lungs, the bone marrow, and the spleen. When the skin, the eye and other organs are involved, the condition may be regarded as secondary." Histologically, the charac-teristic lesion found in tissue removed for biopsy from the skin or lymph nodes is the so-called hard tubercle, a collection of large, poorly-staining epithelioid cells with a scanty marginal zone of lymphocytes, with a few giant cells of the Langhans type, and without caseation. Little direct proof can be furnished through skin tuberculin tests, through the demonstration of tubercle bacilli in the lesions, or through guinea pig inoculation studies that the lesions are truly tuberculous. In the few cases that have come to necropsy, death has been caused appar-ently by miliary tuberculosis and the consensus seems to be that the disease is a peculiar benign form of tuberculosis. However, Snapper expresses his own opinion and that of several other students of the disease to the effect that "Besnier-Boeck's disease must therefore be considered as a peculiar reaction of the reticulo-endothelium with for-mation of pseudotubercles under influence of an unknown virus."

In most of the earlier reported cases of sarcoid the skin lesions were regarded as the primary if not the sole manifestations of the disease. It might be expected that the external structures of the eye would be involved rather frequently. However, only a few cases of sarcoid of

the eyelids, of the conjunctiva, and of the orbital tissues have been reported. In 1917, Derby and Verhoeff⁴ reported the removal of a small painless growth which was situated in the outer third of the lid and ran upward and inward under the orbital margin. Histologic examination proved this growth to be a sarcoid. One discrete nodule of the same type was present on the cheek, but no mention was made of the presence of sarcoids in other parts of the body. At that time, Derby stated: "I have been unable to find in ophthalmic literature any reference to sarcoid, and in a fairly extensive search in the literature of the disease I have not happened upon a case where involvement of the ocular structures was noted." In 1937, Ernsting⁵ reported an almost identical growth which proved on removal to be a sarcoid of the Boeck type. This patient had Roentgen ray evidence of hilar gland enlargement and of sarcoid type infiltration of the lungs and also erythematous lesions on the anterior surfaces of the lower legs which proved on biopsy to be sarcoids of the Darier-Roussy type. Ernsting stated that Lehrfeld reported a case of sarcoid of the eyelid in 1927 and that Friede, Coppez, and Blegvad had reported cases of conjunctival involvement. Blegvad² stated that he could find records of only 8 cases, including 3 of his own (1930). Blegvad described the lesions as small to large chalazion-like tubercles, one to many, studding the conjunctiva, or else clear yellowish speck-like follicles. In 1925, Igersheimer⁶ reported symmetrical tumors of the tarsal conjunctiva of both lower lids which had the histologic structure of Boeck's sarcoid. He stated that Schoeppe had described in this disease small glossy nodules in the ocular and tarsal conjunctiva with small nodules in the tarsus itself and in the iris. In 1939, Walsh²³ stated that "sarcoid of the eyelids has been described frequently. In this situation sarcoid may or may not be associated with involvement of the adjacent tissues, such as conjunctiva, extraocular muscles or orbital tissues." He did not present references to support this statement but includes as an example of sarcoid a case which had been reported by Wilmer in 1933 under the title "Tubercle-like nodules of the episclera and eyelids, bilateral." The patient, a woman, aged 56, presented painless, freely-movable lumps in the eyelids and a mass in the subconjunctival tissue over the right internal rectus muscle. Within 2½ months all the masses had disappeared spontaneously with the exception of one in the lower lid of the right eye. This was excised and showed the histologic picture of "hard tubercle" characteristic of sarcoid. In 1 of the 7 cases of sarcoidosis reported by King, a small firm nodular mass under the conjunctiva projecting into the lower fornix from behind the globe proved histologically to be Boeck's sarcoid. In another case with bilateral kerato-iritis, a sarcoid was found in the skin of the eyelid. Recently (1941), Rosenbaum¹⁶ and Sniderman²⁰ have each reported a case of histologically proven Boeck's sarcoid of the lacrimal glands. In Rosenbaum's case there was enlargement also of the cervical and inguinal lymph nodes. In Sniderman's case there was also bilateral uveitis and enlarged hilar glands by Roentgen ray.

Perhaps of more general interest than these rather isolated instances of involvement of the external ocular structures with growths or nodules of sarcoid type are the lesions of the uveal tract which can be demonstrated to be a part of the disseminated picture of sarcoidosis. King

stated that iritis occurs in 10% of the cases of Boeck's sarcoid. In their monograph, Snapper and Pompen¹⁹ stated: "One of the favorite sites of the disease is the eye; here dissemination of nodules in the iris and in the corpus ciliare explains the frequency with which symptoms of iridocyclitis are found in these patients. As a matter of fact, many of them first consult ophthalmologists and are diagnosed as tuberculous iridocyclitis. Careful general examination may then reveal the presence of other manifestations of Besnier-Boeck's disease. Not uncommonly small nodules of Boeck's disease can be discovered in the conjunctiva in the form of typical yellowish brown nodules." In the series of 13 cases reported in this monograph, iridocyclitis was noted five times, conjunctival nodules twice, and recurrent hemorrhages into the vitreous once.

According to available statistics the actual number of cases of "sarcoid iritis" is not very great. King stated that Osterberg found 26 cases of iritis among 400 cases of Boeck's sarcoid. King noted also that in the 6½ years preceding the publication of his paper, over 1700 patients with various forms of chronic ocular inflammation had been tuberculin tested in the Howe Laboratory. In about two-thirds of the patients, the tests were positive. Among the remaining one-third of cases insensitive to tuberculin (amounting then to between 500 and 600), 7 cases were diagnosed as Boeck's sarcoid. However, the relative infrequency with which cases of iritis or uveitis associated with sarcoidosis are reported in the ophthalmologic literature may well be accounted for by the suggestion contained in the remark of Snapper and Pompen that most of these cases are diagnosed by ophthalmologists as tuberculous.

Some authors believe that the clinical appearances of tuberculous iridocyclitis and of sarcoid iridocyclitis are identical with small nodules in the iris, cloudy media, precipitates on the posterior surface of the cornea, and tendency to the development of posterior synechiae, secondary glaucoma and complicated cataract. Osterberg thinks that, in general, the iritis of Boeck's sarcoid is less painful, less destructive and less proliferative than tuberculous iritis, but that individual cases are difficult to differentiate. Blegvad states that iritis occurs in association with Boeck's sarcoid in one of two forms or phases, the serous or the nodular. In the serous phase, the iritis has no special characteristics other than its frequent association with band-shaped keratitis. The nodular phase or form, however, has characteristics which should distinguish it from tuberculous iritis. Tuberculous nodules in the iris are dirty white or slightly yellowish, almost always quite round or oval with smooth surfaces, and appear to come from deep in the iris, shoving aside the surface fibers. Vessels go around the nodules. When they resolve, residual spots of atrophy of the iris tissue remain. The nodules of Boeck's sarcoid are often very large, are not smooth and round but have an irregular surface, are reddish-yellow in appearance and are traversed by a number of fine branching vessels. They are apparently firmer and harder than tuberculous nodules and may proliferate through the sclera at the limbus. They have a spontaneous tendency to heal and disappear without trace, leaving no residual atrophy of the iris.

King also notes the two types of iritis in sarcoidosis. He states that the serous type is characterized by slight ciliary injection, fine posterior

corneal precipitates and a moderate amount of cells in the aqueous. In the nodular type, the ciliary injection is more marked, the cornea is usually edematous and cloudy, the precipitates on the posterior surface of the cornea are larger and more numerous. In the iris, the nodules are apt to be few in number, are fairly discrete and are invaded by blood-vessels. They are smaller and more superficially situated than the nodules of tuberculous iritis. The clinical course is usually more benign than in tuberculous iritis and healing may occur with complete resolution of the nodules and often with little scarring and slight impairment of vision. However, the course of the iritis may be complicated by corneal opacification and the development of posterior synechiae and secondary glaucoma. In King's opinion it is difficult to distinguish clinically between the ocular lesions produced by Boeck's sarcoid and by tuberculosis, and the differential diagnosis depends usually on the identification of the disease process elsewhere in the body, biopsy of skin or lymph nodes, roentgenographic studies of the chest and bones, serologic studies and tests for allergy. Occasionally, the diagnosis is confirmed, as in one of King's cases, by histologic study of a portion of the iris removed by iridectomy for the treatment of secondary glaucoma. In summary, King states that, "When characteristic changes are revealed by biopsy of the skin, lymph nodes, or bone, and by x-ray; when the Wassermann and tuberculin tests are negative and the constitutional symptoms are relatively slight, a diagnosis of sarcoid becomes as nearly positive as it can be with our present knowledge."

Only occasional reports of involvement of other tissues of the eye in cases of Boeck's sarcoid have appeared in the literature. Chorioretinitis has been mentioned occasionally but usually in association with iridocyclitis. King mentioned the finding in sections of an enucleated eye, which he examined in conjunction with Verhoeff, typical sarcoid nodules in the retina and in the distal portion of the optic nerve. In 1935, Salvesen¹⁷ reported bilateral optic neuritis in a patient with Boeck's sarcoid of the skin of the arms, infiltration of the hilus glands, renal insufficiency, fever, increased sedimentation rate, achylia, secondary anemia, and negative Wassermann and skin tuberculin tests. The optic disks were grayish-red, blurred, and elevated 1 D. Vision was reduced to hand movements. Nine months later the disks were pale and the vision was 5/10 in the right eye and 5/30 in the left eye. In 1938, Roos¹⁸ reported the case of a girl, aged 6 years, with bilateral uveitis and benign lymphogranulomatosis, the diagnosis being established by biopsy of a lymph node. Later, there developed bilateral choked disks of 1 D, drowsiness, three attacks of generalized convulsions, and transient paresis of the right arm and leg. The spinal fluid was under increased pressure and contained increased cells and protein. The girl's condition improved gradually.

In 1931, Reis and Rothfeld¹⁴ described the case of a 17-year-old girl with headache and vomiting, skin sarcoids of the Darier-Roussy type (confirmed by histologic examination), negative Wassermann, negative von Pirquet and Mantoux tests, and roentgenographic evidence of osteitis cystica tuberculosa (Jüngling) and of enlarged hilus glands and of infiltration of the apex of the right lung. There was bilateral exophthalmos greater in the left eye. The vision was ability to count fingers at 16 inches in the right eye and *nil* in the left eye. Ophthalmoscopic

examination revealed in the right eye a choked disk of 5 D with secondary optic atrophy and in the left eye a white tumor mass occupying practically all the retina under the retinal vessels and projecting 20 D into the vitreous. There was slight weakness of the right leg and bilateral positive Babinski's. The spinal fluid showed increased protein. Later, the patient developed loss of memory and mentality and epileptiform convulsions and died in an epileptiform attack. Necropsy revealed at the base of the brain a flat, translucent, yellowish, hard infiltration around the infundibulum, chiasm, and both optic nerves, extending back to the cerebral peduncles and laterally under the temporal lobes, greater on the left. The floor of the third ventricle was markedly infiltrated. Generalized tuberculosis in various stages was found in other organs and tissues. The left optic nerve was markedly enlarged, the sheaths edematous and matted together with local infiltrations of small cells and proliferation of connective tissue with some blood-vessels. The walls of the blood-vessels showed hyaline degeneration or infiltration with lymphoid cells. There were several varying-sized foci of epithelioid cells with marginal zones of lymphocytes without giant cells, necrosis or caseation. The tumor mass consisted apparently of tuberculides somewhat altered by edema.

One of the patients in a series of cases reported by Walsh in 1939 showed, in the right eye, slight pallor of the disk with numerous superficial discrete white dots in the paramacular area with a tendency to perivascular arrangement, and in the left eye, uveitis with marked atrophy of the optic nerve and white spots scattered throughout the fundus. There were bitemporal field defects, but a normal sella. One year later, a mass elevated 8 D was present in the choroid of the left eye. It was considered to be tuberculous. Nine years later there was marked optic atrophy in the right eye with contraction of the temporal part of the field of vision; the left eye was phthisical. The patient had developed diabetes insipidus, but roentgenographs of the head were still normal. The left eye was enucleated and the mass in the choroid proved histologically to be a sarcoid tumor. Walsh also mentioned a case of Vandergrift's, as yet unreported, with bilateral papilledema and sarcoid masses in the brain and meninges.

Aside from the cases mentioned above, there are very few reports of involvement of the nervous system in association with Boeck's sarcoid. According to Roos and Salvesen, Boeck himself mentioned the presence of anesthesia over the ulnar distribution in one arm of one of his patients; Nazza mentioned pain, loss of sensation, muscular paresis and atrophy in the arms and legs proved at necropsy to be due to sarcoid nodules in the nerves; Urban and Winkler found infiltrations around the cutaneous nerves.

Perhaps more frequent in occurrence than the typical "sarcoid iritis" and certainly more frequently reported in the literature are cases of so-called "uveoparotid fever," "uveoparotid tuberculosis," "uveoparotitis" or "Heerfordt's disease." As stated by Longcope and Pierson, the syndrome of uveoparotid fever consists of bilateral uveitis and parotitis preceded or accompanied in the early stages by fever. Later, the disease becomes chronic, the fever usually subsides and other symptoms appear. After many months, recovery usually takes place. Paralysis of the facial nerve is said to accompany the swelling of the

parotid gland in about one-third of the patients, and in one-half of these the facial paralysis is bilateral. Pareses of other cranial nerves may occur or more distant parts of the nervous system may be affected. There may be swelling of the submental, submaxillary and cervical lymph nodes. Occasionally, there are associated skin lesions of varying types, including erythema nodosum. In a few cases, roentgenograms of the chest show increased shadows in the mediastinum or at the roots of the lungs.

Most of the articles on the subject of uveoparotid fever present essentially reports of one or a few cases. However, Savin¹⁸ presents an analysis of the symptoms and findings in 67 cases. The two sexes are almost equally affected and the disease can occur at essentially any age, though it appears most commonly between the ages of 10 and 30. It starts usually with parotid swellings or iritis, but the initial symptom may be a facial or other paralysis or erythema nodosum. The parotid swellings are painless, may last from 6 weeks to 2 years, and do not suppurate. The iritis is at times nodular in type and precipitates on the posterior surface of the cornea are present frequently. Occasionally conjunctivitis is present and, rarely, transparent nodules are found on the ocular and palpebral conjunctiva. In some cases, keratitis has been reported, in 7 cases optic neuritis, in 10 cases opacities in the vitreous and in a few cases choroiditis and hemorrhages in the retina. Facial paralysis occurred in 20 cases and was bilateral in 9. In scattered cases, ptosis, diplopia, paralysis of the soft palate and of the recurrent laryngeal nerve, and polyneuritis of the peripheral type have been reported. Fever was present in 16 cases, erythema nodosum or other skin lesions in 16 and pulmonary tuberculosis in 10. The facial palsy so common in these cases may or may not be due to pressure on the nerves by the parotid swelling. That it is not is suggested by the order of occurrence of the lesions in a case reported by Muirhead.¹³ First, iridocyclitis with secondary glaucoma of the right eye; 2 months later, iridocyclitis of the left eye; 2 weeks later, right facial palsy; 2 months later, left facial palsy, and 1 month later, bilateral parotitis. According to Tait,²¹ the uveitis is insidious and painless in its onset. It is characterized by the production of a typically adhesive exudate, readily producing posterior synechiae of considerable strength and permanency. There are profuse coarse deposits on the posterior surface of the cornea. The vitreous may contain numerous opacities. Secondary glaucoma may develop. In other cases, the iritis may be of nodular type. McCulloch¹² states that the nodules in the iris are small, pale and gelatinous-looking and occur usually at the pupillary margin or on the collarette, occasionally at the ciliary margin.

Arbuse and Madonick¹ list the symptoms of uveoparotid fever under five headings: 1, prodromal—general malaise, weakness, lassitude, drowsiness, anorexia, gastro-intestinal upsets, loss of weight, puffiness of eyelids, long-continued dryness of mouth, dysphagia, cough, night-sweats, pain in the chest, abdomen or joints, paresthesias, polyuria without glycosuria, paralysis of other cranial nerves besides the facial, low-grade temperature; 2, glandular—involvement of the parotids, painless, non-suppurative, is constant; at times enlargement of the

submaxillary, sublingual, lacrimal, cervical and hilar glands; 3, ocular— involvement of the eyes is always present but may vary in type; iritis, cyclitis, or uveitis usually, conjunctivitis, corneal herpes or other forms of keratitis, opacities in the aqueous or vitreous, chorioretinitis, hemorrhages in the retina, optic neuritis or atrophy, neuroretinitis, glaucoma (secondary), and cataract (complicated) occasionally; (4) neurologic— 50% of the cases present some abnormality of the nervous system; facial paralysis is most common; peripheral neuritis, ptosis, involvement of the sensory part of the fifth nerve, dysphagia, loss of taste, hallucinations, meningeal signs, delirium, hypersomnia, convulsive seizures may occur; the spinal fluid may show an increase in cells and protein content; 5, other manifestations—diabetes insipidus, erythema nodosum, xerodermia, papulonecrotic tuberculides, polyarthritis and amenorrhea may occur; the electrocardiogram may indicate myocardial involvement.

Levin¹⁰ listed the neurologic manifestations of uveoparotid fever as follows: edema of the optic disks (at times), partial ptosis, diplopia without complete oculomotor paralysis, involvement of the fifth nerve (sensory portion), the seventh (most common, a peripheral type of neuritis not always due to parotid swelling), the eighth, the ninth or the tenth nerve, peripheral neuritis, diabetes insipidus (rather frequent), hypersomnia, pyramidal tract involvement (1 case), ataxia, headache and vomiting, mild increase in the cell and protein content of the spinal fluid. He stated that the usual course of the disease is toward gradual recovery with postiritic residuals.

This, then, would seem to be a disease with protean manifestations, there being only two requisites for the inclusion of a case in the group, parotitis and some form of ocular involvement, usually uveitis. At the outset, Heerfordt's disease was considered to be a distinct entity in itself, but, recently, it is being recognized more and more widely that so-called "uveoparotitis" is only another manifestation of benign lymphogranulomatosis and that it is essentially the same disease as sareoidosis, but with its most striking symptoms in the eyes and salivary glands rather than in the skin, lymph nodes and lungs. Longcope and Pierson stated that the histologic changes in the lymph nodes and parotid glands in cases of uveoparotid fever are almost precisely the same as in sareoid, miliary epithelioid tubercles with occasional giant cells and with almost complete absence of necrosis or caseation. Garland and Thompson⁶ recognized the same histopathology in this disease but considered the lesions to be tuberculous. They stated: "In one of Heerfordt's cases, a resected portion of the iris showed typical tuberculous lesions histologically—endothelial cells, lymphocytes, giant cells without caseation or tubercle bacilli. . . . In all cases in which biopsies have been performed, whether from the parotids or from the irides, the histologic features have been exactly similar, namely, an endothelial fibrosing tuberculosis in which caseation is absent and tubercle bacilli are not found." One of their patients, a woman, aged 28, with bilateral parotitis, bilateral iridoeyelitis and uveitis and peripheral neuritis, showed at necropsy miliary tuberculosis involving the lungs, pericardium, myocardium, parotid and submaxillary glands, peritoneum, liver, kidneys and uterus.

Bruins Slot, Goedbloed and Goslings³ reported a group of 6 cases of uveoparotitis and of Boeck's sarcoid in which there was a definite intermingling of symptoms in the individual cases. They gave as their opinion that the syndrome of Heerfordt is part of the syndrome of Besnier-Boeck. This opinion is supported, they think, by the histologic changes in the skin, lymph nodes, parotid glands and lacrimal glands. Walsh stated: "It seems unnecessary further to labor the point that uveoparotid fever and sarcoid are similar diseases and may be different manifestations of the same disease." King stated: "Parotid gland enlargement, which occasionally occurs in Boeck's sarcoid, was found in conjunction with uveal involvement in 2 of my cases. Uveoparotitis and Mikulicz's syndrome may both be manifestations of Boeck's sarcoid." With²⁴ stated that uveoparotid fever might be regarded as a special localization of benign lymphogranulomatosis. He advanced in support of this contention the following arguments: 1, the histology is the same—foci of epithelioid cells, few giant cells and little or no necrosis; 2, the bacteriology—prevailing inability to find tubercle bacilli in the tissues and to recover them by culture or by animal inoculation; 3, the glandular enlargements—which may involve any part of the body but are most frequent in the neck and at the hilus of the lungs; 4, infiltrations of the skin of the lupus pernio type have been seen in a number of cases of uveoparotid fever; 5, sarcoid may be limited to the salivary glands and the lacrimal glands with involvement of the uvea; and 6, tuberculin reactions are negative in a high percentage of cases. The greatest point of difference between sarcoidosis and uveoparotid fever lies in the frequency of involvement of the nervous system. Grönblad⁷ is endeavoring to prove that Mikulicz's syndrome, uveoparotid fever and keratoconjunctivitis sicca (Sjögren) are all manifestations of sarcoidosis. Waldenström,²² who mentioned that uveoparotitis may simulate encephalitis lethargica, stated that three characteristics, the tubercular structure without caseation, the large percentage of tuberculin negative cases, and the small number of cases in which tubercle bacilli are found in the lesions, immediately associate uveoparotid fever with another type of granuloma, the so-called morbus Besnier-Boeck." It must be regarded as highly probable that many cases of typical Mikulicz disease with fibrosis and round cell infiltration also represent late stages of the same anatomic process. Waldenström expressed the belief that this process, a universal benign tuberculoid granuloma, is the cause for a great variety of clinical pictures, Besnier-Boeck's disease, lupus pernio, many cases of Mikulicz disease, uveoparotid fever, and cases of so-called encephalitis lethargica with parotitis.

As has been stated previously in this review, there is a widespread, but as yet unwarranted, tendency among writers on sarcoid and on uveoparotid fever to regard both these diseases as unusual or benign forms of tuberculosis. So far, however, it has not been possible to prove definitely the tuberculous etiology of these lesions. Many of the arguments in favor of this view are based on the finding at necropsy of miliary tuberculosis in a patient who has presented earlier clinical evidence of sarcoidosis or uveoparotid fever. Horton, Lincoln and Pinner (quoted by King) report 4 cases of "non-caseating tuberculosis

(type: Boeck's sarcoid)," in 2 of which active uveitis was present and in 1 chorioretinitis and iridocyclitis. In 1 case at necropsy, caseating lesions of miliary tuberculosis were found and they, therefore, suggest that the sarcoids of Boeck represent a non-caseating phase of tuberculosis. A possible explanation for the absence of tubercle bacilli in these "non-caseating tubercles" is furnished by the studies of Kyrle (as noted by King). In experimental tuberculous lesions of the skin, Kyrle found that bacilli were abundant during the first 10 days after injection into the skin but had practically disappeared at the end of 5 weeks. At this time the typical histologic picture of sarcoid was present. Kyrle thinks, therefore, that sarcoid is a distinct type of foreign body reaction to tubercle bacilli and their disintegration products.

The evidence both for and against the tuberculous etiology of Boeck's sarcoid has been well summarized by King. It seems hardly necessary to repeat this evidence in detail in the present review. Those who are particularly interested in this phase of the subject can refer to his original article. Suffice it to say here that King is inclined to believe that the evidence against the tuberculous etiology is the more conclusive.

HENRY P. WAGENER, M.D.

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PHYSIOLOGY.

PROCEEDINGS OF
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Roentgen-ray Diffraction Studies in Iodinated Amino Acids and Proteins. M. SPIEGEL-ADOLF, R. H. HAMILTON, JR., and G. C. HENNY (Department of Colloid Chemistry, D. J. McCarthy Founda-

tion, the Departments of Biochemistry and Physics, Temple University School of Medicine). In order to decide whether "the process of iodinating of the protein also changes the molecular configuration so as to produce physiologic activity" (Salter), Roentgen ray diffraction pictures by the powder method were taken from tyrosine, 3,5-di-iodo-tyrosine, 3,5-di-iodo-thyronine, thyroxine, thyroglobulin, casein, iodocasein, and plastein derived from the latter substance. The Roentgen ray diffraction patterns show that the iodination of tyrosine and 3,5-di-iodo-thyronine brings forth noticeable changes in the diffraction patterns of the resulting substances 3,5-di-iodo-tyrosine and thyroxine. Two diffraction rings (corresponding to spacings of 4.36 and 5.03 Å) are strong in tyrosine and weak in the 3,5-di-iodo-tyrosine diffraction pattern. Conversely, at least two new diffraction rings, non-existing in tyrosine (corresponding spacings at 3.92 and 13 Å) become manifest in 3, 5-di-iodo-tyrosine and persist in di-iodo-thyronine and thyroxine. At least five of the 3,5-di-iodo-thyronine rings (corresponding spacings at 2.12 , 2.37 , 2.60 , 3.04 , 5.57 Å) are absent in thyroxine which alone shows a diffraction ring corresponding to a spacing of 3.62 Å. Effects of iodine presence can be detected neither in thyroglobulin nor in iodocasein. The Roentgen ray diffraction pattern of plastein differs from that of the mother-substance in width of the side-chain and sharpness of the backbone reflection.

An Immunologic Investigation of the Mechanism of Glomerulonephritis. C. F. KAY, P. F. LUCCHESI, and R. B. RUTHERFORD (Department of Medicine, University of Pennsylvania and the Philadelphia Hospital for Contagious Diseases). A synopsis of past and present concepts of the mechanism by which acute glomerulonephritis develops was presented. The relation of certain types of experimental glomerulonephritis to these concepts was briefly discussed. Experiments were devised to determine whether patients with scarlet fever develop antibodies to human renal antigens or streptococcal toxin digests of renal tissue, or whether an unspecified circulatory antigen could be demonstrated to be present early in the disease by the development of specific antibodies at a later period. Complement fixation and precipitative methods were applied to the sera of 78 patients with scarlet fever. The results of these studies were completely negative. These experiments did not support the hypothesis that glomerulonephritis develops as a result of an antigen-antibody reaction. They pertained especially to the recent concept that the antigen concerned may be absorbed or combined with kidney cells or may be kidney cells themselves. Reasons are given why the results of this experiment cannot be taken to exclude the possibility of such a mechanism.

The Use of Sulfonamides in the Prevention of Experimental Brain Abscesses. G. M. MARKLEY (Harrison Department of Surgical Research, University of Pennsylvania). The purpose of this paper is to

report the results on the use of the sulfonamides in the prevention of the experimental brain abscesses.

The technique for abscess production was the same as previously reported except the dose of the bacterial inoculum was increased.

The dose of sulfanilamide, sulfapyridine and sulfathiazole was 0.5 gm. per kilo daily in a single dose by mouth, and that of sulfadiazine was 0.25 gm. per kilo daily. All treated dogs received a course of 5 days of treatment. Determinations of blood concentrations of the various drugs were made daily before the administration of an additional dose. Control experiments were run simultaneously with treatment experiments.

Results: Sulfanilamide protected 66 %, 100 % and 75 % of the dogs inoculated with pneumococcus Type III, *Staph. aureus* and *Strep. hemolyticus* respectively. Sulfathiazole protected 33 %, 75 % and 75 % respectively. Sulfadiazine protected 100 %, 75 % and 50 % respectively. Sulfapyridine protected 100 % of the dogs inoculated with pneumococcus Type III when treatment began before 12 hours after inoculation and 75 % of the dogs when treatment began 17 hours after inoculation. It protected only 20 % of the dogs inoculated with streptococcus and was not used against *Staph. aureus*.

The mean blood concentration of the various drugs of the treated dogs which died was in every instance within the range of the mean blood concentration of the surviving dogs, except for those dogs receiving sulfadiazine. Even so these dogs maintained a mean blood concentration of 20.8 mg. per 100 cc. until the time of death.

Sulfadiazine proved least toxic in these experiments.

Conclusions: 1, Sulfonamide therapy is effectual in preventing pyogenic brain abscesses following injection of pneumococcus Type III, *Staph. aureus*, and *Strep. hemolyticus* into a cerebral area previously traumatized. 2, Sulfonamide therapy should be begun early. 3, Sulfanilamide and sulfadiazine were found to be the most effective compounds.

The Influence of Certain Commonly Used Drugs on the Rate of Gastric Emptying in the Normal Human Subject as Determined by an Intubation Technique. (Atropine, Morphine, Benzedrine, Prostigmine, Nitroglycerine, Syntropan, Meeholyl, Ergotamine Tartrate and Sodium Bicarbonate.) JARRETT H. FOLLEY and W. OSLER ABBOTT (Gastro-Intestinal Section, Hospital of the University of Pennsylvania). The gastric emptying time, as determined by roentgenoscopy under normal circumstances and as affected by drugs, has been frequently determined; but the gastric emptying rate has been more often guessed at than measured. After injecting 500 cc. of dilute milk into the stomach of normal adults it has been possible to quantitate the emptying rate by aspirating, measuring and reinjecting the gastric contents every 10 minutes until 90 % of the initial volume has disappeared. Repeating this procedure 14 times on 5 subjects a total of 70 experiments has been performed, 15 of them controls, 55 exemplifying the effect of varying doses of atropine and of clinical doses of morphine, benzedrine,

prostigmine, nitroglycerine, "syntropan," "mecholyt," ergotamine tartrate and sodium bicarbonate. Although the expected side effects were noted assuring us of the potency of the drug, the results show no significant difference save after morphine when the emptying rate was slowed.

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ORIGINAL ARTICLES.

**AUTO-HEMOLYSINIC ANEMIA WITH AUTO-AGGLUTINATION:
IMPROVEMENT AFTER SPLENECTOMY.**

BY EDWARD H. REISNER, JR., M.D.,

HOUSE PHYSICIAN

AND

MENNASCH KALKSTEIN, M.D.,

ASSISTANT VISITING PHYSICIAN, BELLEVUE HOSPITAL,

NEW YORK, N. Y.

(From the Fourth Medical Division, Dr. Charles H. Nammack, Director.)

THE acute hemolytic anemias may be classed in several groups according to etiology. Among the more obscure of these groups is auto-hemolysin anemia, *e. g.*, acute hemolytic anemia due to the action of auto-hemolysins arising apparently spontaneously within the body. We have recently had opportunity to observe such a case, which presented, in addition to the criteria necessary for the diagnosis, certain other features of unusual interest, which it is the aim of this paper to discuss, along with a review of the literature on the subject of auto-agglutination.

Immunology and Biochemistry. Since there is considerable confusion concerning the nature of auto-agglutination and auto-hemolysis, a few definitions and general remarks are in order. Hetero-agglutination is the clumping of the blood cells of one species by the serum of another species; iso-agglutination, the clumping by the serum of a different individual of the same species; auto-agglutination, the clumping of an individual's cells by his own serum. The cause of the confusion is that the auto-agglutinins when they occur in human serum act, not only on the individual's own blood, but also on all other human blood so that they are really pan-agglutinins. Since they act on the blood of individuals other than the person from whom they are derived they are confused with iso-agglutinins. However, that the action on the individual's cells and other red cells

as well, is due to a single agglutinin, is shown by the observation that the agglutinin can be absorbed out, not only by the patient's cells but by any human blood cells.

The reaction of auto-agglutination is accelerated by cold and retarded by heating and in most cases is reversible at 37° C. It is not to be confused with the exaggerated rouleau formation and clumping—pseudo-agglutination, observed in acute infections, or hyperproteinemia where the erythrocyte sedimentation rate is accelerated.^{19,24a} It is a true antibody reaction and it can be demonstrated that the antibody is adsorbed by the cells.

The source of auto-agglutinins is not clear. Landsteiner and Levine believe that auto-agglutinins acting only at low temperatures exist in most normal human sera and that under certain conditions their titer may become high enough to operate at higher temperatures.^{24b} As pointed out above, these are non-specific agglutinins. What conditions may cause such a rise in the normal auto-agglutinin titer? Some light can be thrown on this question by reviewing the conditions in which auto-agglutination has been observed. A peculiar type of auto-agglutination and auto-hemolysis occurs in paroxysmal hemoglobinuria sometimes encountered in congenital lues. Auto-agglutination has been observed, frequently in hemolytic icterus, in trypanosomiasis, severe anemias, occasionally in pneumonia and even in apparently normal individuals. More recently it has been reported in hemolytic anemia following sulfanilamide therapy¹ and acute hemolytic anemia due to lead poisoning.⁹

In discussing the pathogenesis of acute hemolytic icterus, Dameshek and Schwartz⁵ attribute the disease to the spontaneous formation of exceptionally potent auto-hemolysins and therefore believe that this disease in many instances is a hemolysinemic anemia. They offer no explanation for this sudden formation of auto-antibodies. According to Wiener,^{24d} on the other hand, the auto-antibodies are a symptom and a result of the disease rather than the cause. He believes that under certain conditions which may bring about a sudden massive destruction of the patient's own blood cells, these cells can act as an antigen and stimulate the formation of auto-antibodies, just as occasionally, transfusions of Rh+ blood into Rh- patients may stimulate the formation of anti-Rh iso-antibodies.²⁵ When only a small amount of hemolysis occurs the reticulo-endothelial system can take care of the effete cells, but when large amounts of blood are destroyed the accessory mechanisms of auto-antibody formation are brought into play. However, this process sometimes initiates a vicious circle since the auto-antibodies may dispose not merely of the effete cells, but hemolyze healthy cells as well, and these newly destroyed cells act as a stimulus to more antibody formation. A process similar to this may have taken place in the case herein reported. A similar concept was advanced by Guillain and La Roche in 1909,¹¹ who described the occurrence

in serum and spinal fluid of auto-agglutinins and auto-hemolysins following post-traumatic bleeding into the meninges.*

According to the unitarian hypothesis, hemolysis and agglutination are due to the action of the same antibody under different conditions. This is indicated by adsorption experiments in which agglutinin and hemolysin are removed together. There is also a correlation between the titer of hemolysin and agglutinin.^{24c} Hasser¹² showed that if old cells were used normal iso-hemolysins for each blood group could be demonstrated almost as easily as iso-agglutinins. Therefore, we believe that although they may not always be found without special examination, auto-agglutinins are likely to occur in most cases of auto-hemolysinemic anemia, and conversely, the presence of auto-agglutination in such cases may be so marked as to interfere with the satisfactory *in vitro* demonstration of auto-hemolysins. We believe it more satisfactory to regard these anemias as being due to an auto-antibody reaction.

Efforts have been made by some authors to explain auto-agglutination on the basis of alterations in the chemistry of the blood, particularly with reference to the blood proteins. Thus, this phenomenon is noted as occurring with great frequency in acute infections, multiple myeloma¹⁹ and other conditions. However, as pointed out above, in these conditions the sedimentation rate is greatly accelerated and the red cells have an exaggerated tendency to rouleaux formation, and it is our belief that these instances represent pseudo-agglutination and not true auto-agglutination.

Review of the Literature. Following the discovery of Ehrlich and Morgenroth that a specific antibody reaction could be produced by inoculating a goat with red blood cells from another goat, and the studies on the mechanism of antibody reactions by the same authors, Bordet, Widal, and others, the way was cleared for the recognition of similar and allied phenomena in man. Experimental efforts to produce hemolytic anemias in animals were accompanied by the search to discover cases in man in which hemolysins and hemagglutinins could be recognized as being related to clinical anemia. Although the classification by Landsteiner of the normal iso-agglutinins in human blood was made in 1901,¹⁴ this work did not receive wide notice until it was repeated by Jansky in 1907 and Moss in 1910. The cases reported by observers prior to 1910 as representing auto-hemolysis and auto-agglutination are, in many instances, either obviously cases of iso-antibody reactions or else open to strong doubt.

* In addition, it appears possible that there may also arise specific auto-agglutinins in view of the antigenic properties of red blood corpuscles. Koeplin reported 2 cases with auto-agglutinins, M with pernicious anemia and H with paroxysmal hemoglobinuria and hemolytic anemia.^{15b} Anti-M's red blood cell dog serum was shown to agglutinate only M's and H's red blood cells and no other human red cells. Similarly, anti-H's red cell serum acted only on H's and M's cells. Furthermore, after having agglutinated either one's cells, such sera lost the power to act on the other's. As yet, no one has confirmed Koeplin's work.

The earliest instance that we can find reported in man was in 1890, but it is not well substantiated.⁹ The first case to be described of an auto-hemolysin which was related to an acute hemolytic anemia in man was reported by Chauffard and Vincent in 1909.⁴ An exhaustive review of the reported cases since then has been made by Dameshek and Schwartz in the past year.⁵ In 1908 Widal, Abramé and Brulé,^{23a,b} discussing the differential diagnosis of congenital and acquired hemolytic icterus, stated that the latter was characterized by the presence of auto-agglutinins which were not present in the former, quoted 4 cases, and later described a fifth.^{23c} It is noteworthy that very few other authors of this time reported auto-agglutinins, although several reported auto-hemolysins. Several cases of auto-agglutinins then reported appear to us to be more likely iso-agglutinins and have therefore been omitted from this review.

Since then several cases of auto-agglutination in severe anemias due to various causes have been reported. Roth reported 1 case with pernicious anemia.²⁰ Boxwell and Bigger³ reviewing the problem reported 22 cases in a search of the literature up to 1931, of which 11 suffered from severe anemias, and some of these had syndromes similar to an acute hemolytic anemia. In 1935 Koeplin¹³ reported a case of auto-agglutination with pernicious anemia and another with acute hemolytic anemia¹⁴ and also reviewed the literature reporting 15 additional cases. We have discovered reports of cases in the recent literature by Masters *et al.*¹⁶ (2 cases), Patterson and Smith,¹⁷ Giordano and Blum,⁸ Watson²² (2 cases), Greenwald,¹⁰ Antopol, Applebaum and Goldman¹ (2 cases following sulfanilamide); Gray, Greenfield and Lederer⁹ reported a case following several transfusions for an acute hemolytic anemia due to lead poisoning. Avoiding duplication where possible, this makes a total of 54 cases of auto-agglutination in an extensive (though by no means complete) search of the literature. Undoubtedly this phenomenon is overlooked in many cases, unless its presence is revealed by difficulty in cross-matching or some transfusion accident.

Case Report. This was the first admission of a 43-year-old Chinese restaurant cashier. The family history was negative for anemia or icterus as far as could be ascertained. The past history was negative. The present illness began about a year before admission with migratory polyarthritis of the fingers, hands, shoulders, knees and feet. In June, 1940, the patient sought medical attention and was admitted to the Hospital for Joint Diseases by Dr. B. The positive findings at this time were mild icterus (icteric index 16) and severe anemia with 1.50 million R.B.C. There were hemorrhages noted in the fundi and a palpable spleen. The urine showed numerous red cells and was positive for urobilinogen in 1:60 titer. Four transfusions from carefully matched professional donors were given following each of which he experienced a severe thermal reaction with increased anemia, deepening icterus and gross hematuria. An atypical agglutinin acting on blood of Groups O and A at 20° C. was demonstrated in his blood by Dr. Eugene Katzin and Dr. Philip Levine of the Blood Donor's Betterment Bureau. He had a fever as high as 101.4° F. The erythrocyte count

ranged from 1.50 to 1.31 million, hemoglobin from 7.5 to 3.8 gm. (Sahli). Three blood cultures were negative. An erythrocyte fragility test was not satisfactory due to strong auto-agglutination of the red cells. The blood cholesterol was 156 mg. per 100 cc., cholesterol esters 98 mg. per 100 cc.; the serum proteins were normal; serum calcium 8.7 mg. per 100 cc., phosphorus 4.4 mg. per 100 cc. A bone marrow biopsy showed a hyperplastic marrow filled with erythrocytes and normoblasts. In the middle of August the patient came under the care of one of us (M. K.) and was transferred to this hospital where the studies were continued.

Upon admission to Bellevue the patient's temperature was 100.2° F., pulse 98, respirations 20, blood pressure 130/60. He appeared chronically ill, obese, pale, and slightly icteric. The positive physical findings included slight puffiness of the eyelids, icteric sclerae, and many irregularly shaped hemorrhages with old patches of retinitis throughout the fundi. There was a well-healed biopsy wound over the sternum. The heart was not enlarged to percussion and there was a rapid regular rate and a soft apical systolic murmur. The abdomen was obese and non-tender with the tip of the spleen palpable. Rectal examination revealed a large solitary internal hemorrhoid. The remainder of the physical examination was essentially normal.

Laboratory. The blood count on admission was 1.35 million R.B.C. with 22% Hb. (All hemoglobin values hereafter are Sahli determination—16 gm. equals 100%.) White blood cells were 5600 with neutrophils 78% (Schilling count 0-16-62), lymphocytes 16%, eosinophils 6%, normoblasts 6/100 white cells, erythroblasts 3/100 white cells. There was marked hypochromia, aniso and poikilocytosis with great destruction of red cells in the smear. Many microcytes, some with hyperchromic centers, and macrocytes, Cabot rings, and polychromatic cells were present. The white cells were of normal size, shape and staining. Platelets appeared normal. No parasites were observed.

Further blood studies showed no change in the essential character of the smear. The hematocrit was 10.5%; mean cell volume 70 c. μ ; reticulocytes 24%; platelets 272,800. The bleeding time was 4 minutes, clotting time 21 minutes, with marked clot retraction $\frac{1}{2}$ hour after clotting. The prothrombin time (Smith modification of the method of Quick) was 5 minutes 2 seconds; a normal control was 2 minutes 50 seconds. The erythrocyte sedimentation rate (Wintrobe) was 80 mm. in 5 minutes, but the anemia was so profound that it was not possible to correct for it. The rate was undoubtedly affected by the marked auto-agglutination. Erythrocyte fragility was tested: the bloods of the patient and a normal control were both oxalated, centrifuged, the cells separated, washed in saline, and then centrifuged and resuspended in a 1:5 dilution of saline before being put to the test. Hemolysis began at 0.38 and was complete at 0.34 after 12 hours' incubation. The control values were 0.44 and 0.36 respectively. Clumping of the patient's cells was so marked that it is doubtful if a sufficiently good interface was obtained to allow adequate hemolysis in the higher tubes. Price-Jones curves done by measuring in succession the diameters of 300 cells on each smear showed a biphasic curve with a major peak at 6.8 μ and a minor peak at 8.5 μ . There was a marked broadening of the curve at the lower end of the scale indicating many microcytes.

Blood chemical findings were: NPN 35 mg. per 100 cc.; uric acid 5 mg. per 100 cc.; creatinine 1.3 mg. per 100 cc.; cholesterol 160 mg. per 100 cc.; albumin 3.8 mg. per 100 cc.; globulin 1.8 mg. per 100 cc.; icteric index 18; direct van den Bergh delayed, indirect positive; phosphatase 4.3 Bodansky units; Wassermann negative.

The urine was amber with sp. grav. 1.015; no albumin, glucose, acetone or bile; 2 to 4 red cells per high power field were visible.

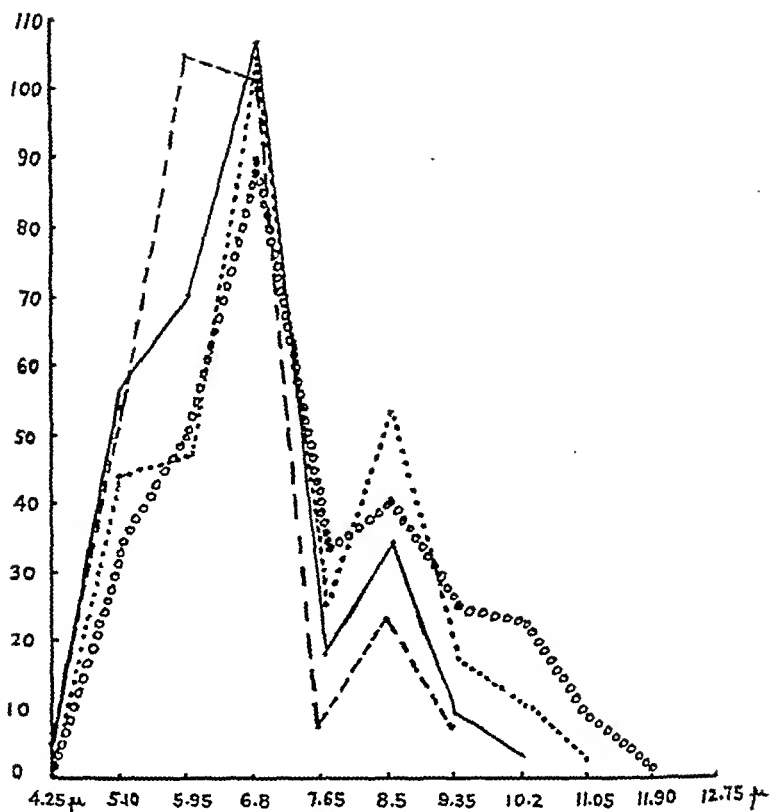


CHART 1.—Price-Jones curves of four different dates plotted on the same graph to illustrate the bi-phasic type of curve, and the shift in relative numbers of microcytes and macrocytes after splenectomy. (Each curve represents direct measurement of 300 consecutive cells on dried smears stained with Wright's stain.) (The curve made up of circles gives erythrocyte diameters 1 week after splenectomy.)

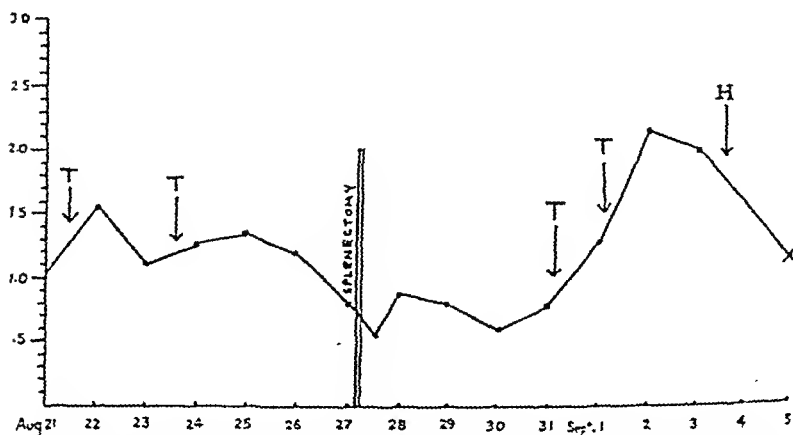


CHART 2.—Graphic representation of the erythrocyte count before and after splenectomy, with special reference to the effects of transfusion. H, indicates onset of rectal bleeding; T, indicates transfusion.

Gastric analysis revealed in the fasting specimen no free HCl, and only 3 units total HCl. One-half hour following histamine there were 37 units free HCl.

The electrocardiogram showed myocardial changes of the Q_2Q_3 type with inverted T_3 interpreted as being due to myocardial anoxia.

The Roentgen rays of the bones and joints of the hands, wrists and knees were interpreted as normal. A 6-foot chest plate revealed some old fibrotic nodules in the right apex and some thickening of the interlobar pleura between the upper and lower lobes on the right. The heart was moderately enlarged in all diameters.

Several examinations of the stools revealed no evidence of parasitic infestation.

Additional Blood Studies. Special hematologic studies were carried out in the Serologic Laboratory of the Office of the Chief Medical Examiner of New York under the supervision of Dr. A. S. Wiener. The tests were considerably hampered by the marked auto-agglutination of the patient's cells. After the blood had stood at room temperature for a few minutes the cells were strongly clumped and an even suspension in saline solution could not be obtained. In contrast to the usual case of auto-agglutination the clumping was not reversed by warming the suspension to body temperature, but an even suspension was finally obtained by washing the cells with saline at 50° C. Unfortunately, this treatment damaged the cells somewhat. The patient was found to be a Group A, sub-group A_1 , type MN whose serum contained auto-agglutinins and also anti-O and anti- A_2 agglutinins, presumably, the result of a previous transfusion from a universal donor and a Group A_2 donor. It was impossible to separate the auto-agglutinins from the red blood cells by centrifuging, washing, resuspending in saline and heating in the usual fashion to body temperature. Because of the intensity of agglutination efforts to determine the presence of auto-hemolysins were unsuccessful, although it was observed that following incubation overnight, there did appear to have been some hemolysis. It was thought that, in addition to the auto-agglutinin and anti-O and anti- A_2 agglutinins there might also be antibodies against the so-called Rh factor recently described by Landsteiner and Wiener^{15,25} but these could not be demonstrated.*

Further Course. From our blood bank 2 bottles of Group A_1 blood, Type M, which showed less tendency to agglutination than any others, were selected. Despite precautions of warming the blood before, and keeping the patient warm during the transfusion of 500 cc., he had a severe chill followed by a rise in temperature to 105.8° . The red blood count rose from 1.02 million (22% Hb.) to 1.53 million (27% Hb.) the next day, but the day after that it had fallen to 1.09 million (25% Hb.). The patient was more deeply jaundiced and his blood showed no trace of the M cells. Another transfusion was given in the same manner with a reaction followed by a transient rise to 1.53 million (27% Hb.) and subsequent fall to 790,000 (20% Hb.) and again complete disappearance of the donor's cells. There was no evidence of hemoglobinuria following either transfusion. After the second transfusion it was felt that immediate splenectomy to remove the chief source of blood destruction was urgently indicated.

* In retrospect, despite the failure to demonstrate anti-Rh antibodies in the patient's serum, Wiener believes that the possibility is not excluded, and that the Rh factor may have played a part in the transfusion reactions. Because of the difficulty in obtaining a good cell suspension it could not be ascertained whether the patient was Rh-minus or Rh-plus. Moreover, it has been found that transfusion reactions due to the Rh-factor can occur in the absence of demonstrable Rh iso-antibodies in the patient's serum.^{24e} In the future when confronted with the same problem we would advise the routine use of Rh-minus donors as an additional safeguard.

On August 27 the patient's spleen was removed together with a small section of the liver for biopsy by Dr. John Morris and Dr. Lester Breidenbach (Fourth Surgical Division). Plasma (250 cc. Type A) was given during the operation and the patient was returned to the ward in good condition. The erythrocyte count postoperatively was 550,000 (15% Hb.); the next day it was 880,000 (22% Hb.).

The spleen weighed 400 gm. The cut section was firm and deep red. The microscopic section showed great congestion of the pulp, with numerous islands of extramedullary hematopoiesis. The liver section showed normal hepatic architecture with islands of extramedullary hematopoiesis and periportal infiltration of round cells and occasional eosinophils.

The course postoperatively was uneventful until the third day when the patient developed a pneumococcus Type I lobar pneumonia in the left lower lobe. Sodium sulfapyridine was given intravenously with prompt fall in temperature and striking improvement within 12 hours. Studies of the blood 4 days following operation showed that the auto-agglutinin titer was still high, but in view of the desperate situation it was decided to hazard a transfusion on the chance that there would no longer be a reaction. A professional donor of Group A₁ was selected and cross-matched and a transfusion of 500 cc. diluted with saline was given in fractionated amounts with no reaction on August 30. The red count rose on September 1 to 1.28 million (34% Hb.) and many normoblasts appeared in the smear. On that day a second donor was used in the same manner with no reaction, and on September 2 the red count was 2.12 million (48% Hb.) and on September 3, 2.03 million (34% Hb.), which indicated that the blood destruction had practically ceased. The auto-agglutinins persisted as before despite the absence of reaction. Normoblasts at this time were 121/100 white cells and this was reflected in the Price-Jones curve which showed a falling off of the number of microcytes and increase in the macrocytic cells. On September 3 the temperature rose and the patient began to complain of abdominal pain and to pass large amounts of chocolate-colored blood by rectum. The white count rose to 39,300 with 98% neutrophils, and following the onset of bleeding the red blood cells fell very rapidly, to 1.13 million (26% Hb.) on September 4. The patient continued to bleed and expired on the ninth postoperative day. Throughout the whole postoperative course there was a tendency to edema which was counteracted by plasma transfusions every few days. Unfortunately, permission for a necropsy could not be obtained.

Discussion. This case fulfilled the criteria usually accepted for the diagnosis of acute hemolytic anemia. The patient showed icterus, anemia, hemoglobinuria at least once at the other hospital, microcytosis and marked evidence of new blood formation with reticulocytosis. The biphasic Price-Jones curve has been emphasized by Dameshek and Schwartz⁵ and demonstrated experimentally by Tiggert²¹ *et al.* as being characteristic of the hemolytic anemias. The question may be raised whether this may have been a case of familial spherocytic jaundice. Both spherical microcytes, and increased erythrocyte fragility have been demonstrated repeatedly in other types of hemolytic anemia^{2,5,7,18,19,21} (clinical and experimental) and there was a negative family history in our case. As far as we could determine there was no evidence of parasitic infestation, or exposure to any toxic agents which could cause an acute hemolytic anemia. Therefore, we regard this as a case of acute hemolytic

anemia due to the spontaneous action of some intrinsic factor, in this case an auto-antibody.

We have stressed the inter-relationship between hemolysins and agglutinins, and we believe that there was a strong auto-hemolysin active in this case, although it was impossible to demonstrate it *in vitro* due to the overwhelming presence of an auto-agglutinin. An unusual feature of this auto-agglutinin was the fact that its action persisted at body temperature and that it could not be split off from the red cells by any methods tried. To the best of our knowledge this is an entirely unique phenomenon which we are unable to explain. The unusually high titer of the agglutinin was probably due to repeated transfusion reactions with hemolysis of blood and liberation of more antigen. The anti-O and anti-A₂ agglutinins demonstrated did not play any further clinical rôle, since the patient received no further transfusion with other than A₁ blood. They probably represent, along with the auto-agglutinin, a heightened capacity of the patient's antibody forming elements to respond to antigenic substance.

The factor which precipitated the initial hemolysis remains unknown, but a vicious circle was established, hemolysis necessitating transfusions which in turn led to increased hemolysis. The only treatment which could break this circle was the removal of the chief site of blood destruction, the spleen.⁶ That this rationale was correct was indicated by the fact that following splenectomy the patient was able to receive transfusions without reaction in spite of the persistence of the high auto-agglutinin titer. This also suggests strongly that the spleen itself was the actual site of hemolysis of the cells on which the hemolysin was adsorbed.

It is a striking testimony to the efficiency of the drug therapy of pneumonia that the patient recovered from his postoperative infection. We had some hesitation about giving the drug in view of its occasional hemolytic tendencies,¹ but we had no other choice because the result of typing was not immediately available. In spite of the drug the red blood count rose until the terminal bleeding episode began. The cause of death is unproven, but the evidence suggests it was due to exsanguination from hemorrhage into the gastrointestinal tract.

Summary. 1. The problem of acute hemolytic anemia due to autohemolysins is discussed with particular emphasis on the phenomenon of auto-agglutination.

2. A review of the literature reveals 54 cases of auto-agglutination. The immunologic aspects of autohemolysis and auto-agglutination are discussed and the more satisfactory concept of the auto-antibody reaction is advocated.

3. A case of acute hemolytic anemia with a strong auto-agglutinin is described. This auto-agglutinin was unique in that it persisted despite warming to 37° C. and could not be separated from the red blood cells.

4. In the presence of the spleen the auto-antibodies caused the destruction of blood cells introduced from without, but following splenectomy, transfusions were tolerated with rise in the blood count, despite the persistence of the auto-antibodies. It would appear from this that splenectomy is the rational therapy in such cases.

The authors wish to express their appreciation to Dr. A. S. Wiener of the Serological Laboratories of the Chief Medical Examiner's Office of New York City for examining the blood of the patient, and for his advice with regard to the preparation of this article.

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CHRONIC LEUKEMIA IN THREE SISTERS.

BY JOHN H. HORNBAKER, M.D.,

ATTENDING PHYSICIAN, WASHINGTON COUNTY HOSPITAL, HAGERSTOWN, MD.

THE following cases of leukemia are of interest because of the occurrence of this disease in 3 sisters, and in an unusual combination, 2 of them clearly being of the lymphatic and 1 clearly of the myelogenous type.

Although familial leukemia has been described a number of times,^{2,3,5,7-9} most of the reports concern but 2 members of a family. There are only a few descriptions of 3 or more cases in one family. McGavran⁶ reported 3 cases of leukemia in one family: 2 brothers, 1 of whom had myelogenous leukemia and the other lymphatic

leukemia, and an uncle on their father's side who had the lymphatic type. Decastello⁴ reports an interesting family, observed by Weiss and himself, 6 members of which had lymphatic leukemia within two generations. Out of 5 brothers and sisters of the first generation, 3 died of leukemia. Out of 9 members of the next generation, 3 died of leukemia, all of them were children of 2 of the 3 members of the previous generation who had died of the disease. Boggian¹ observed a family of 2 brothers and a sister in which 1 brother had 9 children and 3 of them developed lymphatic leukemia, and the sister had 3 children, 1 of which had lymphatic leukemia.

There is insufficient evidence at the present time to explain the occurrence of familial leukemia on the basis of heredity, except for the known heredity factor in cancer, of which leukemia is now usually regarded as an example. However, in view of reports of different combinations of blood diseases in the same family, as well as leukemia, it would seem that some predisposition to abnormality of the blood-forming tissues does exist in certain families. In reviewing the literature it is interesting to note that most of the cases of leukemia occurring in more than one member of a family are of the lymphatic type.

CASE 1.—A white female, who developed purpuric spots over the legs and occasional oozing of blood from the nose in the summer of 1927, when she was 39 years old. In October, 1927, and February, 1928, she had severe bleeding from the nose and mouth and developed purpuric spots over the entire body. These cleared up from time to time but she noted a tendency to bruise easily. She was hospitalized in April, 1928, because of earache, and examination at that time revealed the following: rapid pulse, afebrile, moderate degree of pallor, enlarged lymph glands in the cervical, supraclavicular, axillary and epitrochlear regions, spleen questionably palpable, no purpura at that time, heart and lungs normal. Blood studies revealed: erythrocytes, 3.69; hemoglobin, 80%; leukocytes, 18,500. Differential: neutrophils, 36%; lymphocytes, 64%. A re-check showed: leukocytes, 18,000. Differential: neutrophils, 30%; lymphocytes, 70%. A blood culture was sterile.

She continued to have hemorrhages from the nose and mouth and into the skin, and died in August, 1928, at the age of 40. While postmortem examination was not done, there was no question of the diagnosis of chronic lymphatic leukemia in the mind of the attending physician, who had observed her closely throughout the illness.

CASE 2.—A sister of the previous patient developed general weakness and swelling of the neck glands in the latter part of 1934, at the age of 55. In February, 1935, a blood study revealed: erythrocytes, 3.95; hemoglobin, 68%; leukocytes, 36,800. Differential: neutrophils, 20%; lymphocytes, 80%. Her course continued unfavorably with increasing loss of strength and weight and gradual development of general glandular enlargement. A blood study late in 1935 was said to be about the same as that above. In March, 1936, she was sent to a Baltimore hospital for Roentgen therapy. Examination at that time revealed a poorly nourished female with generalized glandular enlargement. The abdomen was tender throughout and there was a question of free fluid being present. The liver and spleen could not be palpated satisfactorily because of tenderness. No mention of purpura was made. Blood studies on March 23, 1936, revealed: erythrocytes,

3.90; hemoglobin, 76% (Sahli); leukocytes, 153,000. Differential: neutrophils, 2%; lymphocytes, 95%; pathologic lymphocytes, 3%. Another study 5 days later showed: leukocytes, 190,000, with a differential count of 1% neutrophils and 99% lymphocytes. Diagnosis: chronic lymphatic leukemia.

She was given Roentgen therapy over the spleen, inguinal and axillary glands, but her condition became suddenly worse and she died, March 30, 1936, at the age of 56. No autopsy was done.

CASE 3.—A sister of the previous 2 patients was first seen in August, 1939, at the age of 55, with symptoms of 1 year's duration consisting of undue fatigue, blue spots on the body, and loss of 18 pounds in weight. Examination at that time revealed a rather poorly nourished female with a fever of 99.6° F., pulse rate 120, blood pressure 170/100. One small hemorrhage was present in the fundus of the right eye and there were several large ecchymoses on the lower extremities but no fine petechia. No glands were palpable. The spleen was felt at the level of the umbilicus. The remainder of the physical examination was negative. A blood study showed: erythrocytes, 2.57; hemoglobin, 68% (Haden-Hausser); leukocytes, 162,000. Differential: neutrophils, 57%; lymphocytes, 2%; myelocytes, 30%; myeloblasts, 8.5%. She was sent to a Baltimore hospital for Roentgen therapy and was given a total of 796 r units over the spleen from September 21 to September 27, 1939. Blood counts on admission, prior to therapy, were practically the same as those given above. However, additional blood studies were done and are as follows: bleeding time, 2 minutes; clotting time, 3 minutes, 20 seconds; volume index, 1.10; M.C.V., 96.8 c.μ; reticulocytes, 3.2%; peroxidase stain showed 96% granular cells and 4% non-granular; platelets, 318,000; nucleated reds, 2/200.

Ten days after the last Roentgen ray treatment had been given the blood picture was as follows: leukocytes, 11,500. Differential: neutrophils, 60%; lymphocytes, 19%; monocytes, 2%; eosinophils, 10%; basophils, 8%; myelocytes, 1%.

She improved clinically following Roentgen therapy; the spleen was no longer palpable, the ecchymoses disappeared and she felt stronger generally. Through the winter of 1939-1940 her general condition remained reasonably good, although blood counts at frequent intervals revealed a gradual rise in the total leukocytes with increasing numbers of immature myeloid cells. In June, 1940, she was given further Roentgen therapy over the spleen, which had enlarged to 3 cm. below the costal margin. A blood study previous to this treatment was as follows: erythrocytes, 3.72; hemoglobin, 72% (Sahli); leukocytes, 137,500. Differential: neutrophils, 73%; lymphocytes, 1%; monocytes, 1%; eosinophils, 8%; myelocytes, 15%; promyelocytes, 1%. Following treatment the leukocytes dropped gradually to 5700 in July, 1940, and only a few immature cells were noted in the smears.

During the remainder of 1940 her condition was satisfactory except for a bout of low back pain apparently brought on by heavy lifting. Roentgen rays of the spine were interpreted as showing decalcification of the bodies of the lumbar vertebrae but no actual bone destruction or deposits of any kind. The condition improved under appropriate treatment.

Late in December, 1940, the spleen was again palpable to the level of the umbilicus and the liver edge was felt 5 cm. below the costal margin. No glandular enlargement was noted. The blood study showed: leukocytes, 138,000. Differential: neutrophils, 51%; lymphocytes, 2%; monocytes, 1%; eosinophils, 3%; basophils, 5%; myelocytes, 17%; myeloblasts, 4%; metamyelocytes, 17%. In February, 1941, she lost 10 pounds in the space of 3 weeks and developed many ecchymoses over the body and extremities. In March, 1941, she was given further Roentgen therapy, receiving 4 treat-

ments over both the liver and spleen. At the time of the last examination in May, 1941, she felt well generally, the spleen was not palpable, no glandular enlargement was noted and the blood count showed 6650 leukocytes with a practically normal differential ratio. No immature cells were present. Diagnosis: chronic myeloid leukemia.

The remainder of the family history is as follows: the mother died at the age of 73 of heart trouble; the father died at the age of 63 following accidental injury. One sister is living and well and blood counts during the course of a hospital admission in 1939 were normal. Two brothers are living; 1 in good health, and the other suffering from hypertension and stomach trouble. While blood studies are not available on either one there is apparently no evidence of a blood dyscrasia. Case 3 has 2 daughters who are living and well and recent blood studies on both were normal. There was no question of a blood disorder in any of the grandparents, as far as is known.

Summary. An instance of familial leukemia is reported in which 3 sisters have been affected, 2 with the chronic lymphatic type and 1 with chronic myeloid leukemia.

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THE NORMAL PLASMA COAGULATION TIME.*

BY GARNETT CHENEY, M.D.,

ASSOCIATE CLINICAL PROFESSOR OF MEDICINE, STANFORD UNIVERSITY MEDICAL SCHOOL,
SAN FRANCISCO, CALIF.

(From the Department of Medicine, Stanford University Medical School.)

THE coagulation time of reealeified oxalated blood plasma has recently been reintroduced as an important clinical laboratory procedure. It appears to be serviceable as a simple test for vitamin K deficiency.^{1a,4} This test is a modification of "Howell's prothrombin time," which does not measure prothrombin, and it is less complicated to perform than the prothrombin determinations which are now in use. Although the simplicity of this test makes it available for general practice, it must be appreciated that the standardization of the technique of the procedure is on a purely empirical basis, as are all other such procedures, and that the reactions obtained do not duplicate normal physiologic processes.

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The practical general application of a test depends not only upon its accuracy, but upon its simplicity. If it can be shown to be reasonably accurate and serviceable under a given set of conditions, it may justly be used as a diagnostic procedure. In order to meet these qualifications, tests of plasma clotting time must give constant readings in a large group of normal individuals and the physical conditions of the experiment as carried out must not materially alter the results obtained. With this in mind, tests have been performed on the plasmas of 340 normal adults and on 107 patients with non-hemorrhagic disorders. The effect of the technique of venepuncture, the amount of oxalate and calcium added to the blood and plasma, the method of collecting the plasma, and the effect of temperature have been noted in their relationship to the results of the procedure as outlined.

Technique of Test. The test of plasma coagulation time is routinely carried out as follows:

1. A clean venepuncture must be performed, obtaining the required amount of blood in a dry syringe.

2. The blood must be rapidly transferred to a test tube containing a weighed amount of dry potassium oxalate. A number of these tubes may be prepared at one time by adding 2% potassium oxalate and evaporating the solution so that the tube will contain oxalate in the ratio of 10 mg. to 5 cc. of blood. Centrifuge tubes are usually prepared with 5 mg. of oxalate for 2.5 cc. of blood (0.25 cc. of the 2% solution per tube). The oxalate must be thoroughly mixed with the blood by inverting the corked tube 10 or 15 times.

3. The oxalated blood is centrifuged in a constant-speed centrifuge at 3500 r.p.m. for 5 minutes and the plasma pipetted off.

4. Two-tenths of a cubic centimeter of plasma is pipetted into each of 2 small chemically clean test tubes and 0.2 cc. of 0.4% CaCl_2 is added to the first tube and 0.1 cc. to the second. The tubes should be gently shaken 5 to 10 times to secure thorough mixing. They need not be inverted.

A liter of the 0.4% calcium solution may be made up at a time, using chemically pure CaCl_2 .

5. The coagulation time of the plasma should be read in minutes. The end-point is taken when the solution no longer flows when the test tube is held horizontal. The shortest time of coagulation for the two tubes is the plasma coagulation time.

6. The room temperature at which the test is carried out should be recorded. A variation between 23° and 26° causes no gross variation in the test.

7. The test should be completed within the first hour after the venepuncture.

The Calcium Factor. As the test is carried out, sufficient calcium is added to produce the shortest clotting time for the amount of oxalated blood used. This has been determined for the particular technique involved as previously described.^{1a} It is now well recognized that substitution of the same amount of calcium as has been combined by adding potassium oxalate is not satisfactory.³ It is also well recognized that adding an excess of calcium prolongs the plasma time⁵ and adding too little calcium also prolongs the coagulation time or prevents coagulation from occurring.

The Collection of Blood Plasma. Blood plasma may be obtained by allowing the blood to stand until a sufficient volume of cells is settled out to permit pipetting off clear plasma from the upper level of the tube contents. A more rapid and satisfactory method is to centrifuge the oxalated blood which clears the plasma of formed elements. Centrifuging only a few minutes at low speed fails to separate all the cells and platelets from the plasma, while centrifuging 30 minutes at high speed will produce almost a complete separation. As the coagulation time of the plasma depends partly on its content of formed and recently broken up platelets, the time and speed of centrifuging are important factors in standardizing any test of plasma-clotting time. The time and the speed chosen for the test are entirely arbitrary and consequently a constant time and speed must be utilized in order to obtain comparable results. The time and speed chosen were selected because they produce an almost complete sedimentation of cells in a brief period which can be accurately regulated in the Gyro constant-speed centrifuge.⁶ The effect of variations in the speed of a centrifuge is shown in Table 1. The slower rates of 1200 and 1800 r.p.m. tend to shorten the coagulation time because of the higher concentration of thrombokinase; and conversely, the rapid rate of 3500 r.p.m. reduces this concentration and prolongs the time. Similarly, centrifuging at a given speed for a short time shows the same type of effect in coagulation. Such changes are also shown in Table 1.

TABLE 1.—COMPARISON OF SLOWER SPEEDS OF CENTRIFUGING FOR LONGER PERIODS OF TIME WITH THE STANDARD HIGH SPEED OF 3500 R.P.M. FOR 5 MINUTES.

Case No.	R.P.M.	Tube No.	Time Centrifuged.						Control 5 min. at 3500 R.P.M.
			5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	
1	1200	1				5		6	5
2		2				4.5		5	5
		1				6		8.5	5
3		2				5		5	5
		1				9		5	7
4		2				6		5	5.5
		1		7		7			7.5
5		2		5.5		6			5.5
		1		4		6			7.5
6		2		4		5			6
		1	5		4.5			7	8
7		2	4		4.5			5.5	6
	1	4		4				4.5	
8	2	3		3				3.5	
	1	4		6.5				5	
9	2	3.5		5			6	4	
	1	5.5	6	6.5			6	5	
10	2	4	4	4.5				4	
	1	6.5	7.5	7.5				6.5	
11	2	5.5	5.5	5.5				5	
	1		5	6				6	
12	2		5	4				4	
	1	7.5	7	7.5				7.5	
		2	6	6	7.5			7	

Because a high-speed centrifuge may not always be available, lower speed centrifuging for a longer period of time has been carried out in 12 cases to ascertain whether or not comparable results may be secured. The results obtained as shown in Table 1 indicate that plasma coagulation times are comparable when the blood is centrifuged at 1200 r.p.m. for 30 minutes or at 1800 r.p.m. for 15 minutes, as they do not deviate more than 1 minute from the standards set up at 3500 r.p.m.

Nygaard⁴ has obtained plasma for his test of clotting time by allowing oxalated blood to stand 4 hours at ice-box temperature and omitting centrifuging. His tests have been carried out at 37° temperature and his normal figures are considerably shorter than those obtained after centrifuging in the manner described for room temperature. However, 30 samples of plasma obtained in the usual way have been tested for coagulation at 37° as shown in the last column of Table 2. The times have varied between 1.5 and 3 minutes, averaging 2.18 minutes or 130.8 seconds. This average is slightly less than Nygaard's figure of 161 seconds for 57 normal cases read by coagelgram. These findings indicate that the plasma obtained in 5 minutes of centrifuging is grossly comparable to that obtained after 4 hours of settling out at ice-box temperature.

Variations in Temperature. It has long been known that variations in temperature have a marked effect on the clotting of blood and blood plasma. Cold prolongs the clotting time and heat up to a certain degree shortens it. Minot² showed in 1916 that through a range of temperature from 15° to 37° there was a gradual shortening of the time with each degree of temperature. Nygaard has recently shown the same effects with his method of testing plasma-clotting time.⁴ He found that there was a shortening of the time up to 37° C. and that the time tended to become longer at higher temperatures. Consequently he chose 37° as the standard temperature for his test. For the technique of the test already outlined^{1a} room temperature was chosen because it eliminated the use of constant temperature water baths which might not always be readily available and because variations at the usual room temperatures of 23° to 26° C. were sufficiently slight so as not to alter the interpretation of the test. It was readily recognized that the results of the test would be more accurate if run at a constant temperature. However, normal plasma run at room temperature fell within a range of 2 to 8 minutes when the temperature in the laboratory varied between the extremes of 19° and 26° C.

With these variations in mind, a series of 122 normal tests has been run at the laboratory temperatures between 19° and 26° and an additional 28 tests at 27°, 28°, and 29°, and normal standards set up for each temperature. These normal standards for the individual temperatures are presented in Table 2 and Chart 1. It is obvious that the temperature range from 23° to 28° produces very

little change in the rate of clotting, the average variations lying between 4.5 and 5.7 minutes. It is noteworthy that there is a sharp accelerating effect at 29° to 2.7 minutes, and there is a progressive prolongation of the coagulation time from 23° down to 19°, which corresponds to Minot's observations.²

TABLE 2.—VARIATIONS IN PLASMA COAGULATION TIMES AT DIFFERENT TEMPERATURES IN 180 CASES.

Temperature.	No. of cases.	Shortest time.	Longest time.	Average time.
19°	5	7	11	9
20°	13	5	10	8.2
21°	12	4.5	8	7.3
22°	18	5	8	6.6
23°	30	4	8	5.7
24°	20	4	7.5	5.2
25°	20	3	7	4.9
26°	4	4	7	4.8
27°	9	3	6	4.7
28°	8	3	6	4.5
29°	11	2	4	2.7
37°	30	1.5	3	2.18

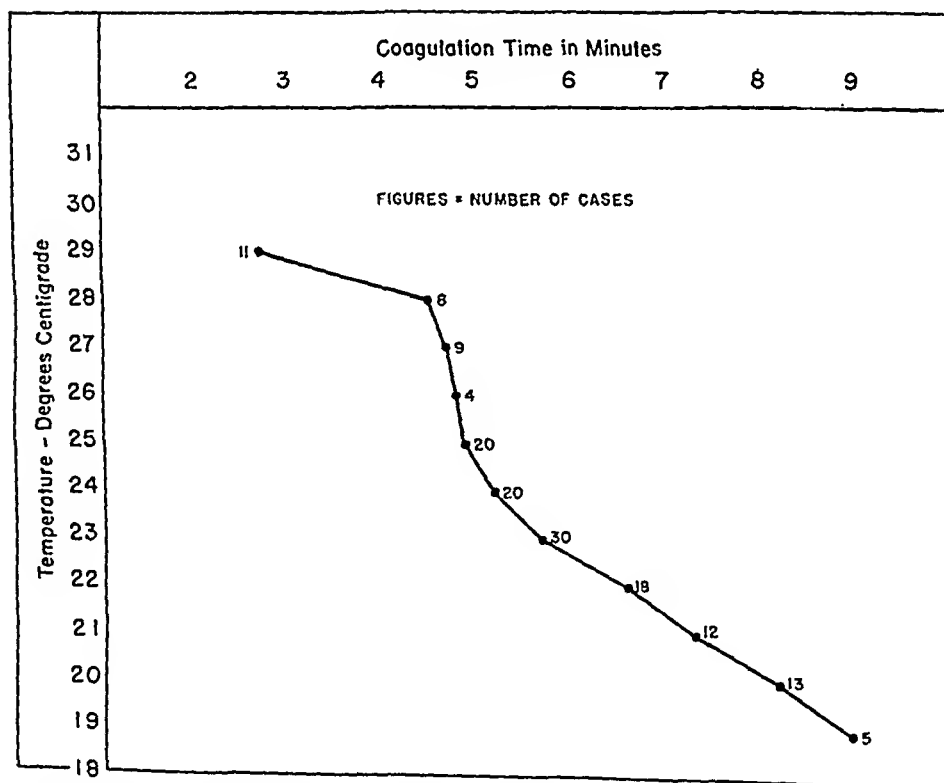


CHART 1.—Relationship of plasma coagulation time to temperature in 122 cases. Variation of less than a minute at the commonly encountered laboratory temperatures of 23° to 26°; progressive prolongation of time at lower temperatures and marked shortening of time at 29°.

In setting up the test at room temperature, it is necessary to appreciate that an apparently slight increase in plasma coagulation

time may be due to an unusually cool room atmosphere and that an apparently short time may be due to an increased temperature in the laboratory occurring in the summer or due to artificial heating. With this in mind, room temperature may be considered satisfactory in carrying out the test, particularly when it lies between 23° and 26° , as the clotting time for 74 cases in this range averaged 5.3 minutes which is to be compared to 5.25 minutes, the average normal time for 340 cases run at room temperature as shown in Chart 2. If a water bath is available to maintain an even temperature of 24° , the results will be more constant. The average time for the 20 cases run at 24° is 5.2 minutes.

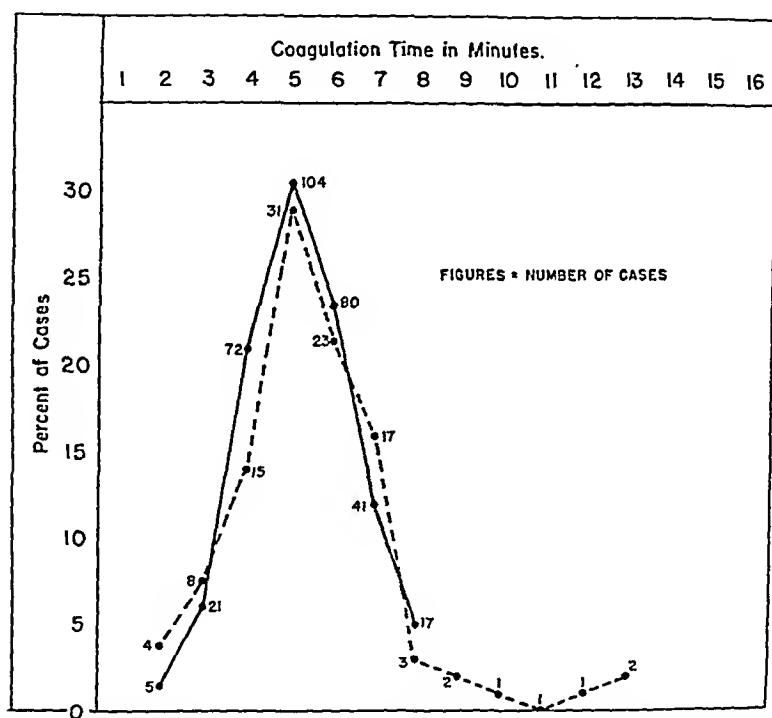


CHART 2.—Distribution of plasma coagulation time by minutes in 340 normal individuals (solid line) and in 107 patients with non-hemorrhagic disorders. Average normal time—5.25 minutes.

The Addition of Thromboplastin. In the test of plasma clotting time no thromboplastin is added. As this substance is an unstable tissue extract, its use complicates the test. It is added in tests of "prothrombin time" to assure an excess of thrombokinas, presuming that as a result a prolongation of the coagulation time will represent a quantitative prothrombin deficiency. This assumption does not take into consideration the concentration of anticoagulant substances in the blood.

The plasma coagulation time actually represents the resultant effect of the relationship of the clot-promoting substances and the clot-retarding substances in a given plasma under the conditions of the experiment. If these substances are out of balance due to prothrombin deficiency, a prolongation of the clotting time will occur and a tendency toward bleeding. However, if a similar deficiency of thromboplastin occurs, clotting time might be prolonged independent of a disturbance in vitamin K metabolism. Actually such a deficiency rarely occurs, and then in the writer's experience only in the presence of marked thrombocytopenia. Two patients out of 23 studied with purpura showed such a prolongation. Both had advanced leukemia with almost a complete absence of platelets from the blood and both showed only slight increases in coagulation time. Nygaard has observed similar cases,⁴ but the clinical and laboratory features of these cases could hardly be confused with vitamin K deficiency, unless they occurred coincident with liver disease and jaundice.

Not only does the addition of thromboplastin appear to be unnecessary, but quantitative diminutions of prothrombin as shown by prolonged "prothrombin times" may not indicate a hemorrhagic tendency. This is well illustrated by the physiologic hypoprothrombinemia of the new-born.

Other Factors Which May Influence the Test. Up to the present time no study of the effect of age of the individual on the plasma coagulation time has been recorded. It is an impression of the writer that elderly people may tend to show a slightly shorter coagulation time than the average normal of 5.25 minutes. Also the possible effects of sex have not been studied statistically but no differences have been noted. However, in running tests of plasma coagulation time on the cord blood of 11 infants, it was found that the average time was only 2.7 minutes and that the limits of variation were between 2 and 3 minutes, except for one reading of 4.5 minutes. It is assumed that this hastening of coagulation was produced by an increase in thrombokinase of cord blood which may readily occur when the cord is cut. Seven observations on 3 infants in the first 3 days of life showed coagulation times from 3 to 6 minutes with an average of 4.4 when the blood was obtained readily by venepuncture. Only a few children have been studied and they showed no variation from normal adults.

Normal Variations. The plasma coagulation time has been performed on 340 normal individuals. This group includes the 100 cases previously reported.^{1a} All the tests run have been incorporated in this series except those run in a water bath at less than 21° or greater than 26° for statistical purposes for Table 2 and Chart 1. The results are presented diagrammatically in Chart 2, which shows the number of cases and percentage incidence for the coagulation time in minutes from 1 to 13. Clotting occurs in 86.35% of the

cases in 4 to 7 minutes with an average for the whole group of 5.25 minutes. This is 0.13 minutes shorter than the normal average of 5.38 minutes already noted,^{1a} but is evidently due to the cases being more evenly distributed throughout the slightly warmer summer months. The majority of the 17 cases with a clotting time of 8 minutes occurred in the winter at temperatures of 21° or below, and consequently this figure should be considered at the upper limits of normal. Table 2 shows that this reading did not occur above 23° and it was only encountered once in the 30 cases read at 23°.

The plasma coagulation time has also been studied in 107 patients with non-hemorrhagic types of disease. For the sake of comparison, the results in this series of cases have been compared to the normal in Chart 2. The trend of the curves is similar with few exceptions. The short time of 2 minutes is more than twice as common and may be due to the inclusion of 3 cases of venous thrombosis in this group. The lower incidence of 4-minute times is unexplained. The appearance of prolonged coagulation times above the normal upper limit of 8 minutes in 6 cases is worthy of comment.

Of the 2 patients with times of 9 minutes, 1 was suffering from prolonged malnutrition and the other was receiving sulfanilamide therapy for a streptococcus sore throat and fever of 39°. The patient with a 10-minute time suffered from severe allergy, and the one with the 12-minute time had a marked chlorotic achlorhydric anemia. The 2 patients with the 13-minute times had disorders similar to the first 2 patients. It is evident that an occasional patient may have a disturbance in plasma coagulation without known liver or biliary tract disease, hemophilia, or purpura which are the recognized disorders which may cause abnormal tests. Such a condition associated with malnutrition and relieved by vitamin K therapy has already been reported.^{1b}

Summary. 1. The plasma coagulation time is a satisfactory test for vitamin K deficiency, as previously noted.

2. The test has been carried out by a standardized technique in 340 normal cases and in 107 with non-hemorrhagic conditions.

3. The importance of a constant speed and time in centrifuging the blood has been emphasized.

4. The effect of changes in temperature upon the results of the test have been pointed out. Room temperature is satisfactory under ordinary conditions.

5. Standards have been set up for laboratory temperatures which may be encountered and for 37° C.

6. The constancy of the results obtained warrants the use of the plasma coagulation time as a simple laboratory test, provided the physical conditions of the procedure are closely adhered to.

The writer is indebted to Miss Thelma Olsen and Miss Elissa Addis for their technical assistance in carrying out the laboratory tests.

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THE EFFECT OF PARITY ON THE AVERAGE BLOOD PRESSURE AND ON THE INCIDENCE OF HYPERTENSION.

By C. E. ISENHOUR, M.A.,

RESEARCH ASSISTANT,

K. KUDER, M.D.,

STATISTICIAN,

AND

L. V. DILL, M.D.,

ASSISTANT RESIDENT IN OBSTETRICS AND GYNECOLOGY,
NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, Cornell University Medical College, and the New York Hospital.)

MUCH has been written concerning the incidence of hypertension and renal and vascular lesions^{2,4,10} in patients whose pregnancies have been complicated by albuminuria and hypertension. The belief that the "toxemias of pregnancy" play a part in the production of these changes has become firmly entrenched in medical thought and literature.

Although the high incidence of patients who have hypertension 5 to 10 years following "toxic" pregnancies has been stressed, no such "follow-up" studies are available on women who have had pregnancies not complicated by evidence of vascular and renal abnormalities.

Several reports^{1,3,11} in the literature have expressed the belief that the "toxemia" syndrome occurs in those patients who otherwise would become hypertensive, but little real evidence has been brought forward to substantiate this impression.

Studies of blood pressure curves for men and women show that both the systolic and diastolic pressures for women exceed those of men after middle age has been reached. It occurred to us that this significantly higher level of systemic pressure might possibly be explained by the inclusion of a certain number of women whose vascular systems have sustained injury during toxemic pregnancies.

The present communication attempts to determine the incidence of hypertension and the average blood pressure in women of varying age groups who have and who have not sustained pregnancies and to determine how such findings can be related to the toxemias of pregnancy.

Materials and Methods. From the case histories of 1800 women who were admitted to the Gynecological service of the Woman's Clinic as in-patients during the years 1933-1940, there were selected 900 records of nulliparous women* and 900 of parous women. These cases were chosen by sequence of history numbers to satisfy the age group quota. Both parous and nulliparous groups were subdivided according to age by decades from 20-29 to 60 or more; each of the age groups contained 200 cases except the groups including patients 60 or more years of age, and here there were 100 cases.

The blood pressure recorded for each case used in this study was obtained by averaging pressures recorded in the history in the same period of each patient's hospital stay and under similar conditions, and usually consisted of: the pressure determined at the clinic visit; the pressure taken in the admission examination to the hospital; the pressure recorded by the anesthetist prior to administration of anesthesia; and pressures from two subsequent visits to the hospital, either in the clinic or on admission. No pressure determinations were included unless they were taken by a member of the interne staff. Cases were discarded where organic disease of the aortic valve, fever, cardiac tamponade, or general debility were present.

In 90% of our cases more than 1 blood pressure was recorded; 60% had 3 or more; and in 45% pressures were taken at different visits to the hospital, some even in different years.

Only those patients were considered hypertensive whose *averaged* systolic pressures were 140 mm. Hg or more and whose *averaged* diastolic pressures were 90 mm. Hg or more. By this method only those patients with persistent elevation of both systolic and diastolic pressures were considered as hypertensive.

Blood pressure determinations were made on all patients by the auscultation method while in recumbent position. The systolic pressure was taken as the point at which the sound first appeared while the cuff was being slowly deflated, the cuff being originally inflated to a level exceeding this figure. The diastolic pressure was considered at the level at which a sharp demarcation of sound occurred prior to the disappearance while deflating the cuff (the beginning of the fourth phase).

An attempt was made to approximate the age, color, and weight of the patient and the type of operation to which she was subjected. Parity was determined by the number of total pregnancies experienced less the number of pregnancies interrupted prior to viability of the child. In this manner no pregnancy interrupted prior to the seventh month was considered to produce parity.

Most patients were weighed on admission to the hospital.

Table 1 shows the averaged systolic and diastolic blood pressures for both the parous and nulliparous women according to age groups.

It is seen here that a slightly higher systolic level is maintained by the parous woman when compared with the nulliparous at all ages save the 20-29 age group where there is a slightly lower level. There is no consistent difference in the diastolic level save in the 30-39 group, where the parous group shows a minimally higher level (Chart 1).

It is of interest that the incidence of hypertension, given in Table 1, shows a slight increase among the nulliparous patients

* Since it was impossible to get a complete series of records for nulliparous women in the 50 to 59 and 60 or more age groups from the Gynecological Service, it was necessary to add to these groups a few records of cases admitted on the Medical and Surgical Services of the New York Hospital. The criteria for use were the same as those described for the remaining cases.

which is consistent at all ages, of least degree in the 40-49 group and greatest degree in the 50-59.

TABLE 1.—AVERAGE SYSTOLIC AND DIASTOLIC PRESSURES, INCIDENCE OF HYPERTENSION AND AVERAGE WEIGHTS OF 900 PAROUS AND 900 NULLIPAROUS WOMEN ACCORDING TO AGE GROUPS.

Age group.	No.	Wt., kg.	Systolic pressure.			Diastolic pressure.			Incidence of hypertension.	
			Av.	S.D.	P.E.	Av.	S.D.	P.E.	No.	%.
Parous.										
20-29	200	59.1	117.8	10.0	± .48	73.4	9.3	± .45	2	1.0
30-39	200	64.8	125.1	11.4	± .55	77.9	8.9	± .42	8	4.0
40-49	200	67.0	135.5	15.4	± .74	82.7	9.5	± .45	36	18.0
50-59	200	67.5	148.0	20.6	± .99	86.8	11.0	± .53	56	28.0
60 or more	100	64.0	161.9	23.2	± 1.55	89.6	11.8	± .79	51	51.0
Nulliparous.										
20-29	200	55.3	119.6	9.5	± .46	73.2	7.1	± .34	4	2.0
30-39	200	58.6	124.3	13.4	± .64	75.7	9.1	± .44	11	5.5
40-49	200	62.7	133.5	20.4	± .98	81.9	11.2	± .54	37	18.5
50-59	200	66.2	144.4	24.6	± 1.17	87.3	13.4	± .64	73	36.5
60 or more	100	60.9	158.0	30.8	± 2.06	90.9	13.0	± .87	51	51.0

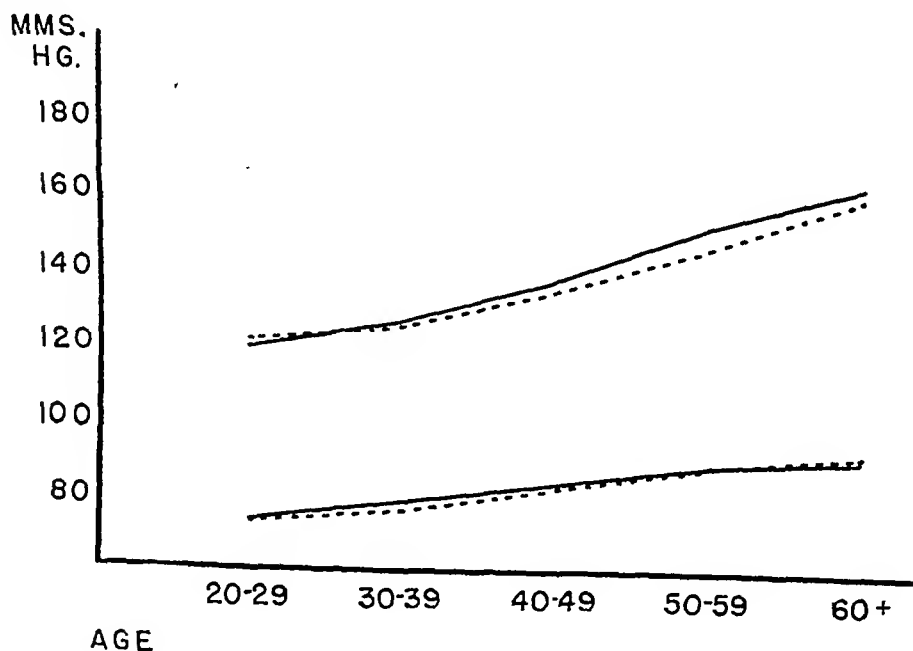


CHART 1.—The average systolic and diastolic pressures for parous (—) and nulliparous (---) women according to age groups.

In order to account for the factor of difference in body weight which might affect the systemic pressure,^{5,12} the averaged weight of each age group is included in Table 1. It is noticeable that the parous woman has a definite and consistently higher body weight than the nulliparous patient (Chart 2).

In an attempt to determine whether repeated pregnancy produces evidence of vascular injury, the parous women were divided into

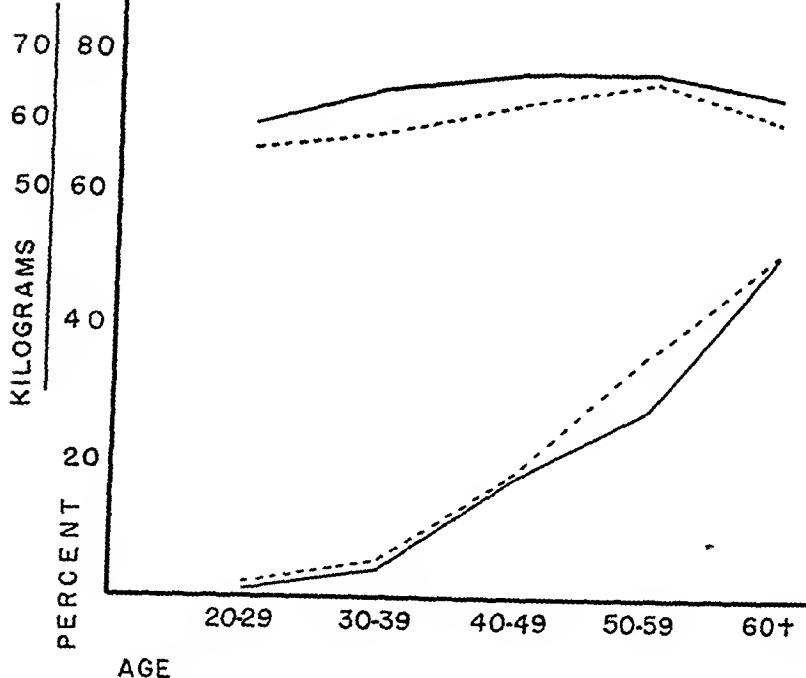


CHART 2.—The incidence of hypertension and the average body weight in kilograms of parous (—) and nulliparous (---) women according to age groups.

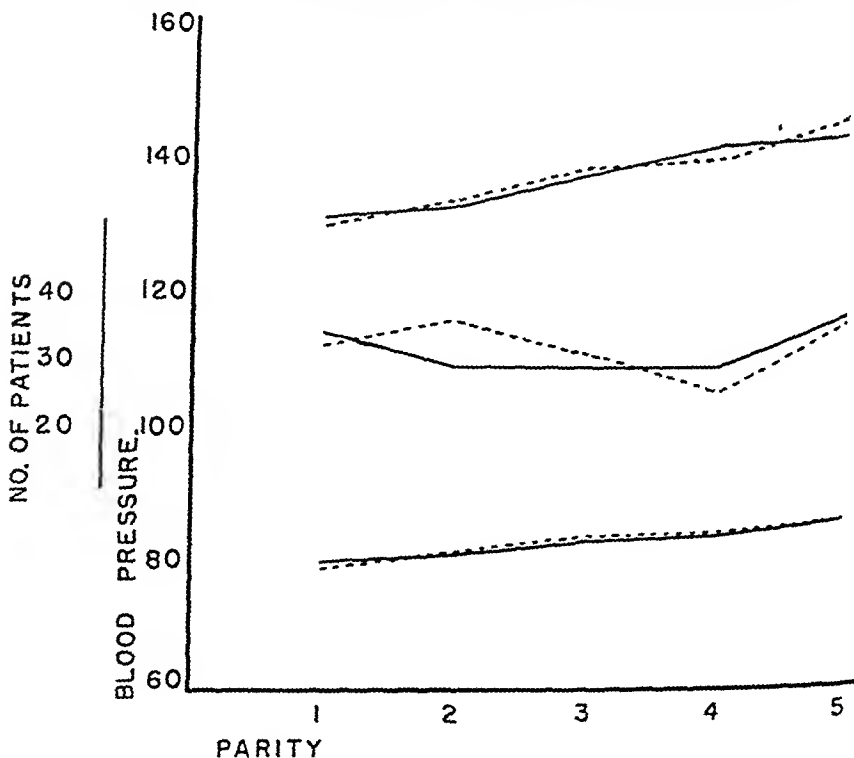


CHART 3.—The actual (—) and expected (---) average systolic and diastolic blood pressures and incidence of hypertension for women according to parity.

groups according to parity from 1 to 4 respectively, with all those having 5 or more parities being included in a fifth group.*

When the actual and theoretical average blood pressures for the parous patients are compared (Table 2), it is clearly shown that both the systolic and the diastolic pressures are closely parallel and that no significant differences can be made out (Chart 3).

The incidence of hypertension in patients of all parities (Table 2) also corresponds closely to the expected incidence for patients of those age groups, and no significant difference with ascending parity can be discovered (Chart 3).

TABLE 2.—THE ACTUAL AND EXPECTED AVERAGE SYSTOLIC AND DIASTOLIC PRESSURES AND INCIDENCE OF HYPERTENSION AMONG WOMEN OF DIFFERENT PARITIES.

Parity.	No.	Actual average pressure.		Expected average pressure.		Incidence of hypertension.	
		Systolic.	Diastolic.	Systolic.	Diastolic.	Actual.	Expected.
1 . . .	277	130.2	79.0	129.0	78.6	33	30.7
2 . . .	234	131.7	80.2	132.9	80.4	29	34.6
3 . . .	151	137.6	82.2	137.8	82.5	28	30.2
4 . . .	113	141.4	83.0	139.3	83.3	28	23.8
5 or more . .	125	142.6	85.3	145.2	85.3	35	34.3
Total . . .	900					153	153.6

Because of a recent demonstration⁶ that the average blood pressure fails to rise significantly with age following the removal from the series of patients who have hypertension, our age groups were recalculated after removal of all patients whose blood pressures averaged 140/90 mm. Hg or more.

It is shown in Table 3 that the systolic pressures following the removal of such hypertensive patients rise constantly in both groups, and that the average pressure for all age groups among the parous women exceeds slightly those levels seen among the nulliparous women.

The diastolic level rises, although more slowly than in the entire series, but fails to maintain its rising level in the parous woman. No more significant effect of pregnancy is noted here than before the removal of the hypertensive patients.

Discussion. The blood pressure levels and the incidence of hypertension in both parous and nulliparous women are well above those usually cited for the male,^{5,12} and it seems reasonable to suppose that the vascular system of the female *per se* has an increased tendency toward this disease.

This work has been done on the assumption that the patients who have elevations of blood pressure are of sufficient number to cause a noticeable increase of the blood pressure level and of the

* The number of patients of each age group was determined for each parity. The average blood pressure of each parity group was then compared with that of a theoretical group composed of cases equally distributed with respect to age. The same procedure was carried out for the incidence of hypertension.

incidence of hypertension in random samples of parous women. To test this assumption it is necessary to determine the expected incidence of hypertension in all parous women if one assumes that some "toxemias of pregnancy" produce residual hypertension.

The "toxemias of late pregnancy" occur in approximately 10% of all women who approximate term.⁹ Of these, 40% to 50% will develop one of the hypertensive states^{2,4,10} (hypertensive disease or chronic nephritis). Therefore one would expect to find from 4 to 5 patients in every 100 parous women in addition to the average incidence for that age group.*

One would therefore expect to find at least 8 patients more with hypertension in each age group when compared with the nulliparous woman.

The average blood pressure level is not such an accurate index to use for determining any addition of small numbers of hypertensive patients to a large group of normal patients. When 4 patients with blood pressure elevations of 40 mm. Hg above the average are added in a group of 100 patients, the absolute rise in level for this group is only 1.5 mm. Hg. A rise of double this amount would be necessary to be of statistical significance (three times the probable error for this method).

We are unable to demonstrate any additional hypertensive patients for any of our age groups of parous women when compared with the nulliparous. This would seem to indicate that if the "toxemias" act as an etiologic agent in the production of hypertension, they do so to an extremely small degree, and that to all intents and purposes the patients having hypertension following "toxemia of pregnancy" are the same patients who would have hypertension had they not been pregnant. It also seems likely that the pregnancy neither aggravates this "latent hypertension" nor makes it obvious earlier, because one finds no increase in the incidence of hypertension in the earlier age groups when these are compared with the nulliparous groups.

TABLE 3.—AVERAGE SYSTOLIC AND DIASTOLIC PRESSURES IN VARYING AGE GROUPS FOLLOWING THE REMOVAL OF ALL "HYPERTENSIVE" PATIENTS IN BOTH PAROUS AND NULLIPAROUS WOMEN.

Age group.	Parous average.		Nulliparous average.	
	Systolic.	Diastolic.	Systolic.	Diastolic.
20-29	117.5	73.2	119.1	72.8
30-39	123.3	76.7	122.1	74.4
40-49	131.5	79.8	127.4	78.4
50-59	140.0	81.8	130.9	80.6
60 or more	146.5	80.6	141.3	81.8

The observation that the most rapid increase in both average blood pressure and the incidence of hypertension is noted following

* This would be obvious only in the group below 50 years of age, for cases above this level would for the most part be absorbed by the high "normal" incidence of the disease in these age groups.

the childbearing period, *i. e.*, at 40 years of age and above, coupled with a failure to find any significant difference in the parous woman when compared with the nullipara in the younger age groups would seem to rule out pregnancy and its complications as an important etiologic factor either in the causation or in the aggravation of this disease.

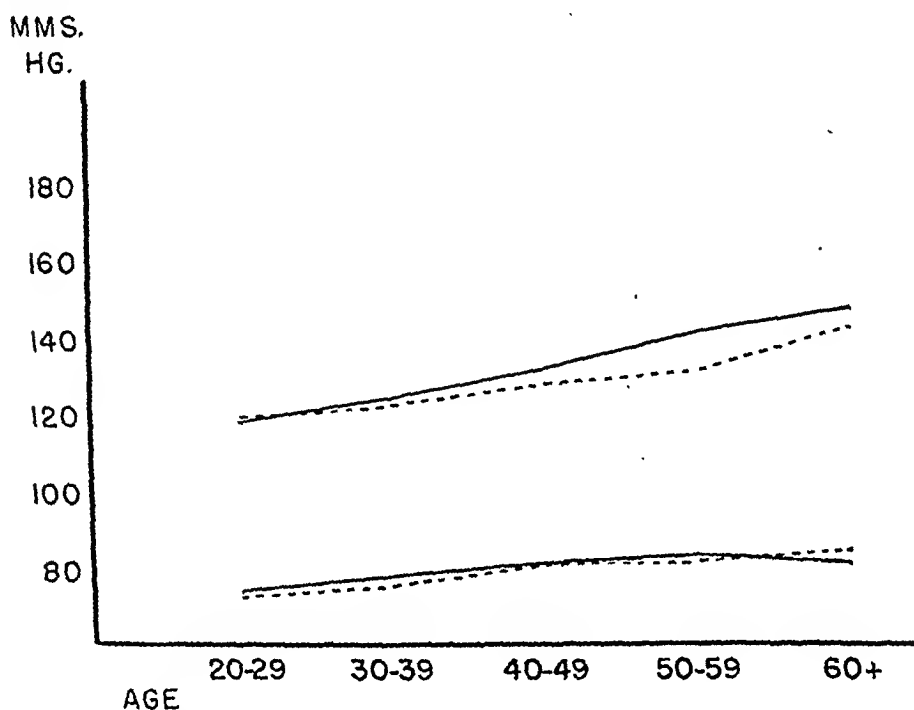


CHART 4.—The average systolic and diastolic pressures for parous (—) and nulliparous (---) women following the removal of all hypertensive cases.

It would seem likely that the apparent minimal increase in systolic level in the parous woman could be explained by the increased body weight which obtains in this group,^{7,8} and the failure to find a similar difference, however slight, in the diastolic pressure would further tend to show that this elevation was not caused by vascular or renal injury as such.

The lack of effect of multiparity on the blood pressure and the incidence of hypertension is of interest. The women who have had repeated pregnancies have not only exposed their vascular systems to the "strain of pregnancy" several times but have also greatly increased their chances of having "toxemia of pregnancy." Despite these factors their blood pressure level and incidence of hypertension is no different from that of the nulliparous patient of the same age.

Following the removal of all hypertensive patients from the group, the average systolic blood pressure still shows a slightly higher range in the parous patient, while the diastolic remains essentially the same. This would tend to indicate that the hyper-

tensive patients present in each group were relatively equal in number and in the degree of hypertension experienced, and that the slightly higher level of systolic pressure among the parous women was not due to the inclusion of a number of "hypertensives."

Conclusions. No demonstrable difference can be noted in the incidence of hypertension and the average blood pressure levels of parous and nulliparous women.

It seems likely that the hypertension and hypertension-producing diseases which occur following a large portion of the "toxemias of pregnancy" are not the result of this complication of pregnancy, but rather that this complication of pregnancy occurs for the most part, if not exclusively, in patients whose vascular systems are endowed with the tendency toward hypertensive disease.

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PRIMARY THROMBOSIS OF THE AXILLARY AND SUBCLAVIAN VEIN.

By LOUIS PELNER, M.D.,

CLINICAL ASSISTANT PHYSICIAN, JEWISH HOSPITAL OF BROOKLYN; ASSISTANT SURGEON,
BETH MOSES HOSPITAL, BROOKLYN,

AND

ISIDOR COHN, M.D.,

ASSISTANT PHYSICIAN, JEWISH HOSPITAL OF BROOKLYN,
BROOKLYN, N. Y.

(From the Department of Medicine of the Jewish Hospital.)

PRIMARY thrombosis of the axillary and subclavian vein is apparently an uncommon condition. Matas¹¹ in his classic paper listed 100 cases that he had found in the literature, and since that time some other cases have been reported. The diagnosis of the condition is not difficult. Kaplan⁸ has listed his criteria for diagnosis, all of which, however, need not be satisfied in a given case. There must, of course, be a swelling and cyanosis of the arm, and dilated superficial veins over the affected arm and anterior chest wall. An increased venous pressure, and prolongation of the circulation time on the affected side are corollaries to be expected from the nature

of the condition. However, these findings are not absolute because they tend to be normalized after the acute phase has disappeared and sufficient collateral circulation has developed. Many of the cases reported did not have the tender cord in the axilla, mentioned as a requisite by Kaplan. The presence of this finding depends on how much of the vein is involved in the thrombosis. Finally, Roentgen ray "visualization" with radio-opaque dyes, and infrared photography of the collateral veins are luxuries in the diagnosis of this condition. An innocuous substance like Diodrast should be used. Certainly there is no need to subject the patient to the injection of the thorium dioxide for "visualization," considering the potential dangers of this substance.

Many of the contributors to the literature of this disease have given their idea of its etiology. In nearly all cases there was a history of some form of sudden injury, often minor. In 2 of our cases there was no immediate antecedent trauma. There are several such cases reported in the literature. Nearly all the cases described were young men in good health. The right arm was more often involved, and when the left arm was involved it was usually in left-handed individuals.

There is a wide diversity of opinion as to the etiology of the condition. Schrötter,¹⁴ who in 1884 first described this condition, thought that it was caused by phlebitis following sudden stretching and compression of the vein. Gould and Patey⁶ found by anatomical study, that there exists a delicate subclavius-axillary valve in the vein where it underlies the subclavius muscle. When the subclavius muscle was suddenly stretched with the arm in abduction, the increase in venous pressure was supposed to have ruptured the valve and resulted in thrombosis. Cadenat³ and Lahaussais⁹ thought that respiratory effort also played a part by distending the axillary and subclavian veins and damaging the endothelium. Lowenstein,¹⁰ working on cadavers, found that in certain of these, when the arm was in an abducted position, the costocoracoid ligament and subclavius muscle indented the axillary vein. This caused a rise in the venous pressure and a distention of the vein. Lowenstein also believed that forced expiration played a part in the slowing of the blood stream. Cottalorda⁴ postulated that trauma produced an irritation of the perivenous sympathetic plexus, with resultant venospasm, and thrombosis. In Cottalorda's case, relief was obtained by excising a segment of the vein involved. In some of the cases described in the literature, thrombi were not found, which makes venospasm a possibility. Rosenthal and Lohr believed that in addition to the mechanical factors, there were also chemical changes in the blood caused by catabolites of abnormal metabolism. This would determine, theoretically at least, which persons would have thrombus formation, conceding a common mechanical basis. Veal,¹⁶ and Veal and McFetridge¹⁷ made a radical departure from

the recorded literature by claiming that on hyperabduction of the arm, the constriction of the vein occurred not over the first rib beneath the subclavius muscle, but below the head of the humerus and against the subscapularis muscle. They included two drawings which showed such a constriction of the subclavian vein at this point. They believed to have experimentally demonstrated that with the arm abducted, and under forced respirations, there were wide fluctuations in axillary venous pressure. This might lead to thrombosis by injury to the vein wall. They did not feel that the venous spasm of Cottalorda was much of a factor in producing the thrombosis.

The physical and laboratory findings in the recorded cases were not all similar. Cottalorda⁴ found both the systolic and diastolic pressure to be higher on the affected side. One worker found no difference in these readings between the affected and unaffected side. Another described a decrease in the systolic pressure, while in the classical case of Matas the blood pressure was increased on the affected side. Horton⁷ found a lowering of the oxygen capacity of the venous blood on the affected side (43 vol. % against 70 vol. %). Lohr found an increased red blood count on the affected side. Matas found a normal bleeding and coagulation time on his subject.

Case Reports. CASE 1.—M. B., a 17-year-old adult male, in apparent good health, observed that in the year previous to admission his entire right upper extremity had progressively increased in width with a concomitant bluish discoloration. After a strenuous basketball game, he noticed a marked engorgement of the superficial veins of the shoulder and arm and felt a sensation of tension and a mass in the right axilla, when attempting to raise his arm. There was no pain or dysfunction. He had always been in good health. Four years prior to this event, while wrestling, his neck was twisted; the head was pulled over to the right for a day, after which he had no further trouble.

Examination revealed that the right pectoral and scapular regions, and right side of the neck appeared much fuller than the corresponding areas on the left. Superficial veins of the right upper extremity and pectoral area were markedly engorged, tortuous and numerous. The hand and arm had a cyanotic flush.

Measurements: right forearm, 28.2 cm.; left forearm, 27 cm.; right arm, 30 cm.; left arm, 28 cm.

Arterial pulse and blood pressure were equal on both sides. Circulation time on both sides was 18 seconds. The venous pressure in the right brachial vein was 34 cm., that of the left was 16 cm. Roentgen rays of the chest, arm and neck were negative.

Venography with Diodrast through the cephalic vein of the left arm revealed normal flow through the vein to the chest wall, which corresponded to the normal site of the subclavian vessel. From then on, all trace of the Diodrast in the vein was lost. On the right side (Fig. 1) the vein was equally well seen up to a point 2 inches externally to the chest wall. In addition, one could see numerous redundant worm-like coils indicative of collateral circulation of the deeper veins of the arm. Also, there was an abrupt blockage of the vein at the normal site of the subclavian, and at this point a collateral vessel into the vein of the neck could be demonstrated. This patient was subsequently seen again 5 years after the onset of the condition. Although the affected extremity was still as large as before,

and the collateral circulation over the surface of the arm and chest wall was still very prominent, the patient had no apparent difficulty in the ordinary use of his extremity.

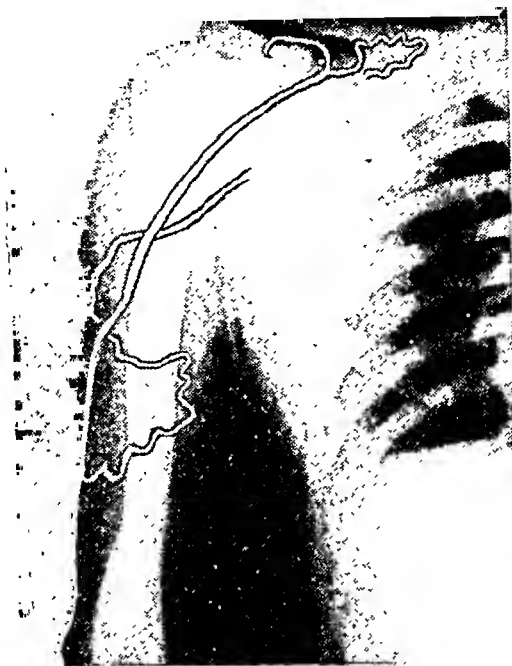


FIG. 1.—Venograph of Case 1, showing the abrupt termination of continuity of the axillary vein about 2 inches from the first rib margin. (Retouched.)

CASE 2.—Y. S., 20-year-old female adult, in good health, suddenly noted a swelling and redness of the right upper extremity 1 week before admission. There was no pain or dysfunction. She had always been in good health, except for a bout of rheumatic fever at 11 years of age which involved her knees and ankles for 2 or 3 months. She was left with no murmurs or other rheumatic stigmata. Three years before admission, she ran into a wall, spraining the right elbow, which was kept bandaged for a few days.

Examination revealed a very well-developed athletic young lady; all physical findings were normal, except for the right upper extremity which showed a non-pitting swelling from the pectoral region to the fingers, and was of a reddish-purple hue. There was no axillary adenopathy, nor was there a tender cord palpable in the axilla. The pulses were equal. The right superficial veins were prominent and tortuous and extended to the right anterior chest wall.

Measurements: right axillary region, 28 cm.; left axillary region, 25 cm.; right midarm, 24.5 cm.; left midarm, 22 cm.; right elbow, 23.5 cm.; left elbow, 22 cm.

The Roentgen rays of the chest, shoulder and arm were negative. Bronchoscopy and laryngoscopy were negative. The venous pressure taken at the cephalic vein on the right side was 24.5 cm.; on the left side, 12 cm. The circulation time by the calcium method on the right was 10.2 seconds, and on the left 8.8 seconds. A Roentgen ray study with Diodrast (Fig. 2), injected at the right cephalic vein, showed pronounced tortuosity of one of the vessels which passed up over the shoulder and into the cervical region.



FIG. 2.—Venograph of Case 2. The axillary vein appears to be thrombosed throughout its entire extent and the collateral veins only are seen. (Retouched.)

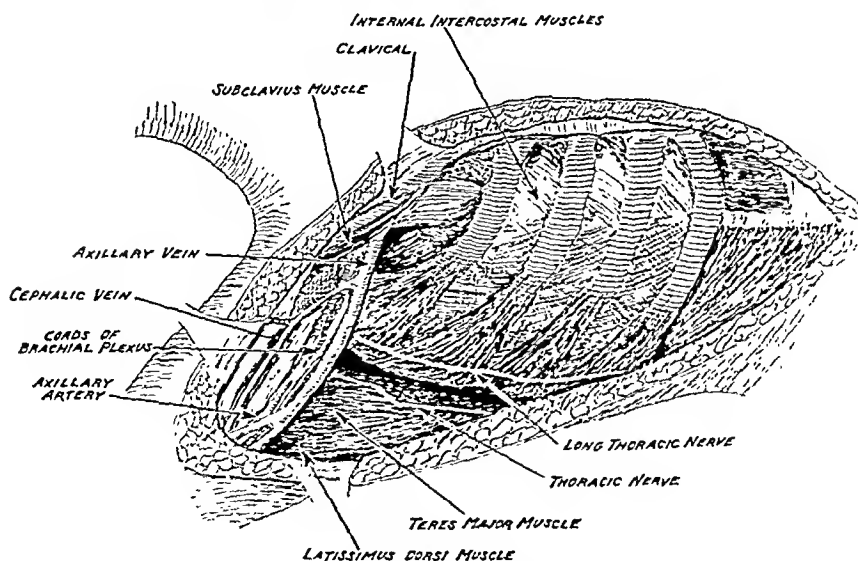


FIG. 3.—Anatomic relations of the axillary vein. Condition found during radical mastectomy operation with upper extremity of the patient abducted and externally rotated. There is stretching of the axillary vein but nearly uniform stretching. (Modified from Cutler and Zollinger, *Atlas of Surgical Operations*, courtesy of The Macmillan Company.)

It was believed that none of the dye had entered the axillary or subclavian vein. The oxygen content of the whole blood was 12.3 vol. % on the right side and 14.8 vol. % on the left side. She was last seen about 9 months after her first hospital stay and showed a slight decrease in the swelling and venous engorgement of the affected extremity.

CASE 3.—I. B., age 23, a well-developed male adult, struck his arm against a wall 3 days before admission. There was some immediate pain, followed by more pain and swelling the following day. For the ensuing 3 days the arm was enlarged and firm.

Examination was negative except for the right upper extremity which showed edema from the shoulder to the fingers, slightly pitting. The extremity was warm and had a mottled appearance.

Measurements: right axilla, 16.5 cm.; left axilla, 15 cm.; right midarm, 12.25 cm.; left midarm, 10.25 cm.; right mid-forearm, 10.5 cm.; left mid-forearm, 8.75 cm.

The Roentgen rays of shoulder and chest were negative. However, they did reveal abnormal, anteriorly placed scapulæ. A Roentgen ray "visualization" of this case was not done. Forty-eight hours after admission, the patient felt that his pain and swelling were relieved and he was discharged. He was not seen subsequently.

Comment. Venous thrombosis may be considered as the product of several factors, more than one of which must usually be present. These are as follows:⁵

1. Change in the vessel wall due to injury.
2. Change in the condition of the blood. This refers to a change in the blood composition and the formed elements of the blood.
3. Change in circulatory condition, such as slowing of the blood stream, the presence of an abnormally low blood pressure, and the formation of eddies in the veins.

1. *Changes in the vessel wall* may be due to injury of the vessel wall itself or to the valve in the vein. Histologically, the vein wall cannot be divided definitely into three coats as can the artery. The endothelium provides the smooth, internal lining to the vessels. The valves are reduplications of the endothelium, and have their free edges in the direction of the blood stream. The vein wall also contains collagen, elastic and smooth muscle fibers. The collagen fibers are somewhat extensible. There is a spiral arrangement of the collagen fibers when the vein has to undergo much functional change in length. Triepel¹⁵ found that certain veins lengthen as much as 50% with body movement, without effect on the venous pressure, but that the resistance rose rapidly when the lengthening reached 55% of the initial size. Here then, we have one cause for the injury to the vein wall; overextensibility beyond the capacity of compensation of the collagen fibers. The elastic fibers are divided into two types; circular, to allow the vessel to accommodate itself to sudden increases in content and later restore normal caliber, and longitudinal to help prevent collapse in certain veins. Rancken¹³ called attention to the fact that while the basilic vein at the elbow can lengthen from 20 to 27 cm., depending whether the arm is flexed or whether it is fully extended; these measurements only hold

true if the vein is not distended with blood. If it is, the vein will become tortuous on flexion. Since most veins are attached to the underlying structures, a sudden deformation of an attached tortuous vein may cause injury to its wall. Stimulation of peripheral nerves usually causes constriction of the veins, *e. g.*, stimulation of the sciatic nerve causes constriction of the saphenous vein. Peripheral nerve injury might cause a prolonged spasm, and slow the venous return in the axillary and subclavian vein.

Valves are an important part of the vein structures. They are reduplications of the intima of the vein, and their free borders point in the direction of the blood stream. The most common position of valves in the venous trunks is just distal to the entrance of tributaries. Valves are found especially in those vessels that are subject to pressure from without, and those in the immediate sphere of muscular performance. The valve closes when the pressure in a segment of a vein proximal to it is greater than distal to it.

Gould and Patey⁶ found a fairly constant valve in the axillary vein under the subclavius muscle, which they thought was delicate enough to be injured if the arm was forcedly raised. Speaking generally, a valve is a very difficult thing to injure, because of its situation and arrangement. The competence of valves and their integrity is guarded against by the pressure of the overlying structures. However, the possibility of the accident does exist.

Veal and McFetridge,¹⁷ on the basis of a thorotrast Roentgen ray examination of one of their cases, came to the conclusion that hyperabduction and external rotation of the humerus causes a constriction of the axillary vein below the head of the humerus, and against the subscapularis muscle. In their study of fresh autopsy material they noticed that the vein was stretched proximal to the point of constriction. It was the good fortune of one of us (L. P.) personally to assist in two radical mastectomy operations and thus be able to test the theory of Veal and McFetridge in the living specimen. With the axillary vein exposed and on hyperabduction and external rotation of the humerus, the vein was seen to stretch, but the narrowing was not at one point, as indicated by these authors, but more uniformly distributed throughout the length of the vein (Fig. 3). This fact was checked many times in these patients. In both of these cases, there was apparently a subclavio-axillary valve present as demonstrated by lack of back flow when the axillary vein was stripped from this point.

In the case of Veal and McFetridge, the blockage of the vein occurred at a point between the situation of the head of the humerus and subscapularis muscle. In one of our cases in which contrast radiography of the venous system was done, and indeed in most of the recorded cases, the thrombus occurred in the subclavian vein at the inner border of the first rib. In another case that we have

described above, the thrombus had apparently extended throughout the entire axillary vessel so that it was not visualized at all in the contrast Roentgen ray. However, it is not for any one to say that a blockage at the point mentioned by Veal is impossible, but it certainly is not the only or usual point as is claimed by him.

Besides the factors enumerated above, mention must be made of several cases of severe venous spasm reported in Franklin's excellent monograph.⁵ A severe venospasm, if it lasts for an appreciable length of time may so slow the venous circulation, as to be at least one factor in thrombosis of the vein.

2. *Change in the Condition of the Blood.* The following alterations in the blood, consequent on tissue injury are important, in the cause of venous thrombosis.¹

(a) Increase in the number of platelets and their tendency to clump together.

(b) Rise in fibrinogen concentration and its effect on the sinking rate of cells.

(c) Anhydremia by increasing the viscosity of the blood. However, important as are these factors, local tissue injury of the vein is necessary to produce thrombosis. These changes in the blood are purely local at the site of thrombosis, as examination reveals normal bleeding and coagulation time and platelet count.

3. *Changes in the Circulatory Conditions.* The factors which influence the bloodflow in the veins of the body are: the *vis a tergo* from the left ventricle, the suction effect of respiratory movements, the muscular support and massage of the vein wall, the support by the abdominal muscles, and the effect of gravity above the cardiac level.

The most important factor in slowing the venous stream in the absence of cardiac failure, is some radical change in the normal variations in the sub-atmospheric pressure of the thorax. In the Valsalva experiment, which consists of a forced expiratory effort with the glottis closed at the end of deep inspiration, the tractive power of the elastic lungs is superseded temporarily because of the high pressure in the respiratory system. The intrathoracic venous pressure rises and the venous return is seriously hindered. According to Moritz and Tabora¹² and Bürger,² the venous pressure rises to 400 to 500 mm. of water during the Valsalva experiment. In everyday life, defecation, parturition, coitus and coughing constitute modified Valsalva experiments. The normal venous pressure varies between 40 and 110 mm. of water. In the excitement stage of anesthesia, there is also a considerable increase of venous pressure.

As regards the influence of exercise on venous pressure, Bürger differentiates two types: prolonged activities of speed and delicacy which have little effect on the venous pressure, and extreme efforts of short duration which have a marked effect. In the latter type,

which is demonstrated by weight lifting, high jump, diving, and swimming under water, there is closure of the glottis at the end of inspiration and contraction of the expiratory muscles. This results in the compression of the thoracic content and the heart. The venous return is markedly impeded and there is marked rise in venous pressure. This description duplicates the conditions of the Valsalva experiment.

In the first 2 cases that we have reported in this paper, it would appear at first glance that none of the three factors discussed, *i. e.*, vein injury, blood changes, or circulatory slowing, are operative. However, both had sustained accidents several years before, which probably left them with some slight injury of the vein wall. At some fortuitous moment of circulatory slowing (any of the everyday duplications of the Valsalva experiment) this combination of injury and stasis could result in thrombosis. The third case had a definite pertinent injury, preceding the thrombosis, as seems to be true of most of the cases in the recorded literature. While this condition is called either "primary" or "effort" thrombosis in the literature, the appearance of some definite cases without immediate antecedent injury has tempted certain authors to label this condition as "so-called" effort thrombosis of the axillary and subclavian veins. We are of the opinion that an injury more or less violent probably antedates most of the cases, but this injury need not immediately precede the thrombosis.

Summary. 1. The literature concerning primary or effort thrombosis of the axillary and subclavian veins has been reviewed.

2. Three personally observed cases, 2 of which were accompanied by venography, were described.

3. The possible causes of this condition were evaluated.

4. Two of our patients could *not* recall any injury immediately preceding the onset of the condition, but did give a history of injury sometime before the thrombosis.

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THE EFFECT OF A BARBITURIC ACID DERIVATIVE ON THE LOBELINE CIRCULATION TIME.

BY KURT BERLINER, M.D.,

ASSOCIATE CARDIOLOGIST,

AND

ALFRED LILIENFELD, M.D.,

ADJUNCT CARDIOLOGIST, SYDENHAM HOSPITAL,

NEW YORK, N. Y.

(From the Department of Cardiology, Sydenham Hospital.)

IN a previous paper,¹ one of us (K. B.) reported his experience with alpha lobeline hydrochloride as an agent for measuring the velocity of bloodflow, a method originally proposed by Teplov and Sor.¹⁸ Lobeline stimulates the respiratory center, probably by way of a reflex from the carotid sinus, and thus produces cough. The reliability of the test, therefore, would seem to depend on the normal functioning of the respiratory center. In clinical medicine, a number of drugs are frequently employed which are known to depress the respiratory center. It occurred to us that the administration of such drugs might influence the results of the lobeline test. The present study was undertaken in order to determine the existence of such an influence. As a drug suitable for this investigation, a rapidly acting barbiturate, sodium propyl-methyl-carbonyl allyl barbiturate (Seconal*)¹⁷ was chosen.

Method. Fifty patients were used in this study; 38 males and 12 females. The patients varied in age from 14 to 75 years (average age 33). Seven were patients suffering from heart disease; 5 of these were in congestive heart failure. The remaining 43 patients suffered from various other conditions such as are commonly encountered in a general medical ward. All patients were in bed. None had fever. The tests were made in the morning between breakfast and lunch.

The technique of the test has been previously described in detail. Only a brief description need be given here: 3 to 5 mg. of alpha lobeline hydrochloride (0.3 to 0.5 cc. of the 1% solution†) are rapidly injected into an antecubital vein. Several seconds later, the patient coughs. The time interval from the beginning of the injection to the onset of coughing represents the "circulation time" for that patient. If cough fails to appear, the test is repeated with 7.5 to 10 mg. of the drug, 10 to 15 minutes later.

In the present study, Seconal was administered by mouth immediately after the successful completion of the test. Thirty patients received 0.18 gm., while 20 received 0.27 gm. After an interval varying from 30 to 90 minutes (usually 60 minutes) the degree of hypnotic effect of Seconal was noted and the lobeline test was repeated. It was found that the hypnotic effect of 0.27 gm. of Seconal was frequently not greater than that of 0.18 gm. This is not surprising since a number of other factors (age, weight, speed of absorption, and others) were operative. Therefore, the patients were divided into three groups according to the degree of hypnotic effect produced, and not according to the dose of Seconal given. Group 1

* Manufactured by Eli Lilly and Company.

† The ampules of alpha lobeline hydrochloride used in this study were supplied by the Sandoz Company.

included those patients who were found to be awake at the time of the second test. Group 2 included those patients who were found asleep at the time of the second test, but who awakened at the touch of the examiner. Group 3 comprised those patients who remained asleep until insertion of the needle. A few patients in this group actually slept throughout the entire procedure.

In each case, the results of the first and second lobeline test were compared and the difference was expressed in terms of percentage of the first result.

In addition, duplicate tests were made on 100 patients without administering Seconal. The time interval between these duplicate tests varied from 15 to 60 minutes. These tests, which are reported in detail in a separate paper,⁹ served as a control series.

Results. The difference in lobeline circulation time before and after the administration of Seconal was striking in most instances. Table 1 shows the results obtained in each of the three groups described above.

TABLE 1.—RESULTS OF LOBELINE CIRCULATION TIME TEST BEFORE AND AFTER THE ADMINISTRATION OF SECONAL—50 CASES.

GROUP 1 (minimal hypnotic effect).				GROUP 2 (light sleep).				GROUP 3 (deep sleep).			
Case No.	First test (sec.).	Second test (sec.).	% difference.	Case No.	First test (sec.).	Second test (sec.).	% difference.	Case No.	First test (sec.).	Second test (sec.).	% difference.
1	5.1	7.5	+ 47	1	11.1	14.3	+ 29	1	16.4	66.0	+302
2	7.5	8.2	+ 9	2	10.1	13.0	+ 29	2	16.0	20.3	+ 27
3	13.6	10.0	- 27	3	11.2	10.6	- 5	3	10.4	70.0	+573
4	9.5	5.2	- 45	4	8.1	8.4	+ 4	4	15.0	40.0	+167
5	8.0	4.8	- 40	5	4.1	5.6	+ 37	5	11.0	12.9	+ 17
6	17.4	17.6	+ 1	6	10.0	12.3	+ 23	6	8.2	52.4	+539
7	10.0	8.1	- 19	7	4.4	5.4	+ 23	7	12.4	17.2	+ 39
8	15.9	10.3	- 35	8	7.9	10.1	+ 29	8	8.4	12.0	+ 43
9	8.1	8.0	- 1	9	15.9	16.5	+ 4	9	3.0	9.0	+200
10	7.2	4.9	- 32	10	7.5	8.2	+ 9	10	12.1	16.7	+ 38
11	8.2	21.2	+159	11	5.6	10.8	+ 93	11	8.9	10.9	+ 22
12	17.7	18.5	+ 5	12	7.4	9.5	+ 28	12	8.2	failure	-
				13	7.2	24.1	+235	13	5.0	18.4	+268
				14	7.6	10.2	+ 34	14	27.9	12.8	- 54
				15	20.5	failure	-	15	9.2	19.9	+116
				16	8.8	25.2	+186	16	6.0	12.6	+110
				17	4.9	6.0	+ 22	17	45.0	23.0	- 49
				18	12.8	44.0	+244	18	11.3	failure	-
				19	17.2	24.8	+ 44				
				20	6.6	9.7	+ 47				

Only in Group 1 (minimal hypnotic effect) were the differences between the first and second lobeline circulation time relatively minor, and only in this group was the second circulation time shortened more frequently than it was prolonged (shortened in 7 cases by an average of 28%, prolonged in 5 cases by an average of 44%).

In Groups 2 and 3, where actual sleep was induced, considerable differences between the results of the first and second test were found in most instances, and there usually was marked prolongation of the second lobeline circulation time. In Group 2 (light sleep), 18 out of 20 cases showed prolongation after Seconal, and the average degree of prolongation was 62%. In this group, the second circulation time was shorter in only 1 case (by 5%), and in 1 case, the

second test resulted in failure. In Group 3 (deep sleep), 14 out of 18 cases showed prolongation of the lobeline circulation time after Seconal, and the average degree of prolongation was greatest (176%). In this group, the lobeline circulation time was shortened after Seconal in 2 cases (by 54% and 49% respectively); in 2 additional cases, the second test resulted in failure.

In the control series of duplicate measurements, where no Seconal was administered, the average difference between the first and second test was 31%. The result of the second test, furthermore, was higher about as frequently as it was lower (higher in 44 cases, lower in 41 cases, identical in 3 cases). Besides, the differences in results were for the most part minor. The greatest single difference in results of the control series was 199%, while after Seconal, prolongations of as much as 573% occurred (in Group 3).

TABLE 2.—COMPARISON OF SECONAL SERIES WITH CONTROL SERIES.

	No. of cases.	Results of both tests identical.	Second test a failure.	Results of second test higher.		Results of second test lower.		All cases, average difference between first and second test.
				No. of cases.	Average difference between first and second test.	No. of cases.	Average difference between first and second test.	
Control Series (no Seconal given)	100	3	12	44	37%	41	19%	31%
Seconal Series:								
Group 1 (min. hypnotic effect)	12	0	0	5	44%	7	28%	35%
Group 2 (light sleep)	20	0	1	18	62%	1	5%	59%
Group 3 (deep sleep)	18	0	2	14	176%	2	52%	160%

Comment. The contrast between the Seconal series and the control series (Table 2) furnishes striking evidence of the effect of Seconal. If we compare the results obtained in each of the three groups of the Seconal series (Table 2), we find additional evidence of seconal effect. In Group 1 (minimal hypnotic effect), the average difference between the first and second test is not great and shortening of lobeline circulation time occurs about as frequently as prolongation. With more marked hypnotic effect, however, the average difference between the first and second test rises progressively, and shortening of the second lobeline circulation time becomes exceptional.

Our results, therefore, lead us to conclude that the administration of a barbiturate such as Seconal prolongs lobeline circulation time.

An explanation of this prolongation is found if we consider the mode of action of each drug. The first, lobeline, is known to stimulate the respiratory center,¹⁶ probably by way of a reflex from the carotid sinus.⁷ One of the manifestations of such stimulation is cough. The second drug, Seconal, belongs to that group of hypnotics which depress the centers in the brain stem, particularly those

of the thalamic and subthalamic regions by which the state of sleep is induced. Vital centers in the medulla such as the respiratory, cardiac, and vasomotor centers are simultaneously depressed.¹¹ Pharmacologic experiments on cats show that the respiratory center is the one primarily and predominantly affected.^{3,4} When a single sublethal dose of one of the barbiturates (sodium ethyl [1-methyl butyl] thiobarbiturate*) is employed, the first undesirable effect is sudden cessation of respiration; only after repeated doses are cardiovascular effects in evidence.¹³ The heart action does not stop unless respiration ceases. As a rule, death is due to respiratory failure.^{5,12} While there may be differences in action between the individual members of the barbiturate group, they all, including Seconal, depress the respiratory center. Thus, they counteract the effect of lobeline, and it is undoubtedly this counteraction which results in the delayed cough response to alpha lobeline. In addition, there is experimental evidence to show that drugs of the barbiturate group depress the carotid sinus.^{2,10,19} This would also interfere with the effect of lobeline.

At this point, the question may be raised whether the prolongation of lobeline circulation time found by us is really caused by depression of the respiratory center, or whether it is caused by actual slowing of the velocity of bloodflow. Experimental evidence is available to answer this question. Schröder and Böckmann¹⁵ recently investigated the effect of two barbiturates on the velocity of bloodflow. These authors produced deep anesthesia by intravenous injection of Eunarcon (sodium bromallyl-isopropyl-N-methyl-barbiturate) in 5 patients, and by intravenous injection of Evipan (methyl-cyclo-hexenyl-N-methyl barbituric acid) in 5 additional patients. The circulation time was measured by Koch's fluorescein method⁸ before, during, and 6 hours after anesthesia. Prolongation of circulation time was never found; shortening was found occasionally.

It is fair to assume, therefore, that the prolongation of lobeline circulation time found by us does not represent an actual slowing of bloodflow, but rather a prolongation of reaction time. This interpretation is borne out by the not infrequent occurrence of inordinate prolongation (up to 573%) of lobeline circulation time in Group 3 of our series, since such extreme slowing of bloodflow could hardly occur.

From our observations, certain conclusions of practical significance may be drawn. Measurements of circulation time by means of lobeline should not be made on patients who are under the influence of barbiturates or other drugs (*e. g.*, morphine) which depress the respiratory center. Since such drugs are used very frequently, this constitutes a definite limitation of the usefulness of the test. Similarly, the lobeline test should not be employed in the presence

* Sodium pentothal.

of pathologic states which are associated with Cheyne-Stokes breathing or other forms of depression of the respiratory center. This second limitation is particularly regrettable, for it had been hoped that the lobeline test, because of its objective end point, would be useful for the measurement of circulation time in conditions such as cerebral accident, uremia, diabetic coma, etc.

Moreover, what applies to lobeline also applies to any other method of measuring velocity of bloodflow which depends for its result on the respiratory center or the carotid sinus. Such methods include the sodium cyanide test¹⁴ and the carbon dioxide inhalation method.⁶ None of these tests should be employed when there is reason to believe that the respiratory center is depressed either by drugs or by pathologic states.

At this point, another comment may be in order. Barbiturates are widely used, and it is commonly assumed that ordinary hypnotic doses have no appreciable effect on the respiratory center. The results of our study, in which such doses were used, indicate that the depressant effect on the respiratory center is greater than is generally appreciated. In this connection, Cheyne-Stokes breathing should again be mentioned. Patients exhibiting this type of breathing are usually restless and sleep poorly. They, therefore, frequently receive barbiturates in considerable amounts. Our observations indicate that this medication may intensify the respiratory disturbance. It would appear that caution in the use of barbiturates is advisable in such cases.

Summary. 1. The lobeline circulation time test was performed in 50 patients, before and after the administration of Seconal.

2. In 12 patients, hypnotic effect of Seconal was minimal. In these, shortening of the lobeline circulation time occurred more frequently than prolongation, and the difference between the first and second test were, for the most part, minor.

3. In 20 patients, light sleep was produced. In 18 of these, the second test showed the lobeline circulation time to be prolonged by an average of 62%.

4. In 18 patients, deep sleep was produced. In 14 of these, the second test showed the lobeline circulation time to be prolonged by an average of 176%.

5. In a control series of 100 duplicate measurements of lobeline circulation time without administration of Seconal, shortening was found as frequently as prolongation, and the average difference between the results was only 31%.

Conclusions. 1. Seconal, a derivative of barbituric acid, prolongs the lobeline circulation time.

2. This prolongation is due to the depressant effect of Seconal on the respiratory center and the carotid sinus. It does not, therefore, represent a true slowing of bloodflow but rather an increase in reaction time.

3. The lobeline test or any other method for measuring circulation time which depends on the respiratory center or the carotid sinus for its result (sodium cyanide test, carbon dioxide inhalation method) should not be employed on patients whose respiratory center is depressed either by drugs (barbiturates, morphine) or by pathologic conditions, especially when Cheyne-Stokes breathing is present.

4. Ordinary hypnotic doses of a barbiturate may depress the respiratory center to a greater extent than is generally appreciated.

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ELECTRIC CONVULSION THERAPY IN PSYCHOSES.

By DOUGLAS GOLDMAN, M.D.,
CLINICAL DIRECTOR, LONGVIEW HOSPITAL,

AND

E. A. BABER, M.D.,
SUPERINTENDENT, LONGVIEW HOSPITAL,
CINCINNATI, OHIO.

CONVULSIONS artificially produced by drugs such as camphor, metrazol (cardiazol), triazol, ammonium chloride, nitrogen, and picrotoxin have now been used in treating psychoses for some 6 years.^{1,3,5,7,11,14,15} During the last 3 years such treatment has been carried out on a large scale in the United States. The chief drug used has been metrazol. Its advantages and disadvantages, as well as dangers, are well known as are also the frequent disappointments and the occasional brilliant results following its use. At this time it can be definitely stated that convulsive therapy has achieved for itself a definite niche in the therapeutic armamentarium of those physicians concerned with mental disease.

In 1937 two Italian investigators, Cerletti and Bini^{1,5,6} described

the use of electric current to produce seizures in dogs. After preliminary study of the technique of the use of the current as well as of the pathologic effects on the brains of animals these workers produced seizures in patients with schizophrenia. As pointed out by Furst,¹⁰ there was some previous work on the use of electric current to provoke unconsciousness and seizures, but the Italian investigators deserve credit for initiating this technique in mental disease. The work was very soon taken up by English, German and American workers.^{9,10,12,13,16,17}

Apparatus and Technique. The technical structure of the apparatus will not be discussed in detail. The earlier apparatus was so arranged that a testing current, which was a fractional part of the treatment current, was passed through the head of the patient to measure the electrical resistance of the patient's tissues. Following this the treatment current was calculated and administered for an accurately measured interval. The current used was 60 cycle A.C. suitably modified by transformers, etc. The newer apparatus, such as that used by the authors, consists of interlocked testing and treatment circuits. The testing current used is 1000 cycle A.C. current of approximately 0.1 milliampere which is imperceptible to the patient, not polarized, and accurately measures the resistance of tissues between the connected electrodes. Setting of the testing circuit automatically sets the treatment circuit to the desired intensity. An automatic electronic timer, variable from 0.05 to 1.0 second controls the duration of the delivered treatment current. The current used in treatment is 60 cycle A.C. as in the older apparatus. The machine includes safety devices which prevent the passage of too high a current or stray current through the patient and which prevent the passage of treatment current before testing current through the patient.

In administering the treatment the patient is made to lie down in bed, a pillow is placed under the dorsal region of the spine to hyperextend to some extent the vertebral column. Electrodes are applied fairly high in both temporal regions. It is not necessary to shave the hair from this portion of the head. Electrode paste such as is used in electrocardiography and electroencephalography is applied to the areas under the electrodes, or a gauze sponge saturated with 10% salt solution is used for electrical contact between the electrode and the scalp. The apparatus is set for the desired time interval, usually 0.2 to 0.5 second. The testing current is applied and adjusted to a level usually between 400 and 600 milliamperes and then the treatment current is applied. The patient's hands and arms are held flexed and adducted over the chest to prevent dislocation and injury to the shoulders. The thighs and legs are mildly restrained and, if possible, a soft cotton and gauze mouth gag is inserted into the mouth during the ensuing convulsion. The management of the convulsion itself is, therefore, exactly the same as the management of a metrazol seizure. The level of the current and the time interval in which it is applied must be experimentally determined at the time of the first treatment. We now routinely use 450 M.A. for 0.3 second as an initial dose because almost all patients will have seizures with this dose. The seizure itself is notable for the brevity or complete absence of the latent period in most instances. Occasionally, however, a latent period of as much as 30 to 40 seconds between application of current and convulsive seizure has been observed. Failure to produce a convulsion was formerly a frequent annoyance, but the newer apparatus seems to be without such fault. The earlier apparatus made to deliver no more than 500 M.A. was rightfully but unnecessarily too conservative. The newer apparatus delivers up to 700 M.A. which is apparently adequate

in the most electrically resistant patients. Occasionally application of the current fails to produce a major seizure, and results only in brief "absence" or "petit mal" type of automatic activity for some seconds. In such instances it is our practice to repeat the current after one minute at a higher level or for a longer period to produce a seizure. The duration of the seizure varies from 30 to 90 seconds and is usually shorter than the average metrazol seizure. The treatments have been given once or twice weekly in the group treated to date. Other types of apparatus were used in the earlier period of this work. Some used constant amounts of current with only time variable, this up to several seconds.

Curare (Bennett) has been used successfully to reduce the force of muscle contractions with electric shock in a number of patients who previously had suffered bone injuries during metrazol treatment in our own or other hands.

Our approach to this work was extremely conservative both in number of patients and in the frequency of seizures produced for the first 8 months. After this preliminary period, we have practically substituted the use of electric shock for metrazol in convulsive therapy. The number of patients in our series is, therefore, not so large as might be expected from our early association with this work.

The ease of producing a convulsion is to a great extent determined by the resistance of the patient's tissues to the passage of current. Certain factors have been found to have a definite influence in this respect. In extremely hot weather when the patient's skin is moist and the conductivity of the skin as a whole is greatly increased it is much harder to produce a seizure. This is apparently the result of the by-passing of a large portion of the current through the skin of the body so that relatively less and definitely insufficient current passes through the head to affect the brain. Under such conditions it is probably wise to postpone for some days any attempt to use this treatment. The use of air-conditioned chambers where they are available may be an answer to this difficulty. In colder weather where the skin resistance of the patient is increased it is sometimes (rarely, however) difficult to pass sufficient current through the head at all to produce a seizure. Under such circumstances the difficulty may be overcome by rubbing the electrode jelly more vigorously into the scalp or using more liberal libations of salt solution in the sponge between the electrode and the scalp. The intensity of the current can be raised somewhat and the duration of the application increased. The electrically produced convulsion differs slightly from that produced by metrazol. There is usually no latent period between application of the current and tonic phase of the epileptiform seizure. Only rarely is there a lapse of 5 to 10 seconds between current application and seizure. In a few instances latent periods of 20 to 40 seconds were observed. The convulsive movements are perhaps less violent in a certain proportion of cases than with metrazol, but this is certainly not always the case. The duration of the convulsive period between onset of

the tonic phase and the first long post-convulsive breath, is definitely less in the electric than in the metrazol convulsion if averages of a series of cases are considered. Convulsive periods as long as 93 seconds have been observed, however. Patients awaken more rapidly and with less confusion as a rule after electric than after metrazol seizures. There is complete amnesia for the period of the treatment and a short period before and after. Our most intelligent patients state that practically no sensation accompanies the treatment and they willingly return for subsequent treatments. It is only after several treatments that patients usually realize that placing the electrodes initiates a series of events for which they have no memory but the awakening.

TABLE 1.—RESULTS OF ELECTRIC SHOCK TREATMENT OF PSYCHOSES.

Duration, yrs.	Complete recovery.	Social remission.	Improved.	Unimproved.
<i>Schizophrenia.</i>				
0-1	1	2	9	1
1-2	0	3	2	1
2-5	1	2	8	5
Over 5	1	1	8	4
Total	3	8	27	11
<i>Manic Depressive and Involuntional.</i>				
0-1	3	1	1	0
1-2	0	0	1	0
2-5	0	0	1	1
Over 5	2	0	2	1
Total	5	1	5	2
<i>Other Diagnoses.</i>				
0-1	1	0	1	0
1-2	0	2	0	0
2-5	0	0	0	0
Over 5	0	2	0	0
Total	1	4	1	0
Total all diagnoses	9	13	33	13
Total patients who completed treatment, 68				

Complications: Dislocation of the jaw has been observed, but this is considered inconsequential because mandibles usually replace themselves or are easily pushed back into place. One fracture of the head of the humerus has been produced. No other major fractures of vertebral or long bones have occurred with electric seizures in our series even though numerous Roentgen ray examinations have been made. The lower alveolus with the four incisor teeth was found fractured after a seizure in one patient but since this patient was violent and self destructive at all times and since no reasonable mechanical relationship between the seizure and the fracture could be adduced this fracture is not considered due to the electric shock. No dislocation of the shoulders has been seen.

The most outstanding feature of the treatment is the total absence of fear of the treatment on the part of the patients who have had one or more treatments. Most of the patients repeatedly and willingly come to the clinic for the treatment and lie down voluntarily on the bed and allow the electrodes to be applied. This statement, of course, does not apply to patients who are negativistic and resistive to any procedure whatever, whether painless or not. After a series of treatments there seems to be less confusion developed than after a similar number of metrazol seizures. In only one instance did secondary seizures occur one or more hours after the treatment. This was in a woman with history of seizures in childhood. Effects on the heart mechanisms seem to be no different than those experienced from metrazol treatment.²

As might be expected, the results from electric convulsion therapy are hardly different from those which have been observed following metrazol. Early in our work with this treatment we used only patients who had been ill for long periods and whose prognosis was hopeless. Our figures, therefore, do not reflect the best that the treatment offers. The figures of our results (Table 1) and our clinical impressions from experience with this treatment lead to the following somewhat dogmatic assertions:

1. Convulsion therapy with electric shock (as with metrazol) is most effective in manic depressive psychoses of either manic or depressive preponderance, involution psychoses, and in some catatonic states.

2. Convulsion therapy only occasionally produces lasting benefit in hebephrenic or paranoid schizophrenic patients.

3. The results of treatment are favorable in inverse proportion to the duration of illness. Duration over one year of any psychosis is likely to be unfavorable.

4. In our experience no unfavorable effects on the psychoses have been produced by the treatment but progress of deterioration in old patients has been unaffected. No clinical evidence of irreversible neurologic damage has been encountered.

We have not thus far seen any patients whom we think have been made worse by the treatment or who have suffered any serious or permanent injury therefrom. No late complications have as yet been observed but we have been giving the treatment for only one year (April, 1941), and have treated 102 different patients with the production of 569 seizures.

Comparison between the electrical convulsions and those produced by metrazol from a therapeutic point of view is of some interest. The outstanding difference between the two methods of treatment is, of course, the relative absence of fear on the part of the patient of the electric seizure. This is, no doubt, due to the almost instantaneous effect of the current and to the complete amnesia of the patient for any part of the treatment. There is some retrograde

amnesia so that the patient does not usually remember even lying down and having the electrodes applied, and the awakening from the electric convulsions is more rapid and quiet as has been mentioned. The therapeutic results of the two methods seem to be practically parallel as far as expectations in the group treated can be considered. Electricity can produce seizures without the difficulty or danger attending intravenous injections. This is to be considered a distinct advantage.

Conclusions. We have completed electric shock treatment on 68 patients suffering from various psychoses. Nine were regarded as recovered; 13 had a "social remission;" 33 more were regarded as improved, and 13 as unimproved.

This interesting therapeutic method must still be considered experimental and not be generally applied without great caution and circumspection. Patients submitted to the treatment should be observed for a long period afterward to determine the possibility of late complications. If these should be no worse than the effects of metrazol, electric convulsion therapy must be considered a distinct adjunct to our present methods.

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THE ASSIMILATION RATE OF INTRAVENOUSLY INJECTED GLUCOSE IN HOSPITAL PATIENTS.

By JAMES C. CAIN, M.D.,

FELLOW IN MEDICINE, MAYO FOUNDATION, ROCHESTER, MINN.,

AND

WILLIAM P. BELK, M.D., F.A.C.P.,

DIRECTOR OF LABORATORIES, THE EPISCOPAL HOSPITAL, PHILADELPHIA, PA.

(From the Wards and Laboratory of the Episcopal Hospital.)

IN 1917, Sansum and Woodyatt,¹ and Wilder and Sansum,² found that the intravenous glucose tolerance limit in man and experimental animals was approximately 0.85 gm. per kilo per hour. The sub-

jects studied were normal, injections were continued over long periods of time, and the rate of injection was carefully controlled by a special pump. An 18% solution of glucose was used in most experiments, but it was found that wide variation in concentration did not influence the tolerance limit. When the rate of infusion exceeded 0.85 gm. per kilo per hour, glycosuria appeared promptly. With the higher injection rates, although glycosuria was constant, the amount of glucose lost in the urine was only a fraction of that injected, and by no means the total amount in excess of 0.85 gm. Glycosuria was observed to stop within a few minutes after discontinuing the injection. Under conclusions (1) they state: "For any individual case the rate at which glucose enters the blood determines the rate of glucose utilization and excretion" Very probably others have conducted similar studies since these reports were published, but we have been unable to find such references by a search of titles.

The object of the present study was to observe the intravenous glucose assimilation rate in hospital patients, and to learn to what extent this should be taken into account in the practical administration of glucose by vein for the maintenance of fluid balance and other purposes.

Method. The subjects studied were adult patients on the surgical service of Dr. E. T. Crossan. Weights were determined by estimate, or by questioning. Glucose was administered by an ordinary gravity apparatus, the rate of injection being calculated from the total amount given and the time consumed in the process, although every effort was made to keep the flow constant. Urine was collected for a period of 12 hours from the beginning of injection, and the amount of glucose excreted was determined by the method of Folin and Wu as for blood sugar, after treatment with Lloyd's reagent.

The more important data are recorded in Chart 1. Case 22 was found, on autopsy, to have a carcinoma of the pancreas and is thought to have been diabetic, although he did not have glycosuria or fasting hyperglycemia. His data were not included in the calculations. Observations are arranged in order of increasing injection rates of glucose per kilo per hour. Grams of glucose retained per kilo per hour are calculated by difference from grams given and grams lost. The chart shows grams of glucose given per kilo per hour plotted against grams retained per kilo per hour.

Discussion. The coefficient of correlation for grams of glucose given and grams retained is very high, 0.9898. This is in agreement with the statement of Sansum and Woodyatt quoted above, that the rate of injection determines the rate of utilization. The maximum utilization rate when a considerable quantity of glucose was given (Case 21) was 5.77 gm. per kilo per hour, or 87 gm. in 20 minutes. The assimilation of 18 gm. per kilo per hour when 25 gm. were injected in 1 minute (Case 22) is regarded too acute an experiment to be typical.

Of equal importance for the purpose of this study is the observation that there was essentially no correlation between the rate at which glucose was injected and the amount lost in the urine. The coefficient of correlation was 0.1063. All cases lost some glucose. This is not in agreement with the observations of Sansum and Woodyatt who found the rate of loss to be determined by the rate of injection, and who observed no glycosuria with low injection rates. That there should be glycosuria in all cases seems understandable, however. The injection of 100 cc. of 5% glucose would, by calculation, raise the level in 5000 cc. of blood from 100 to 200 mg. per 100 cc., at which concentration some glucose must reach the kidneys

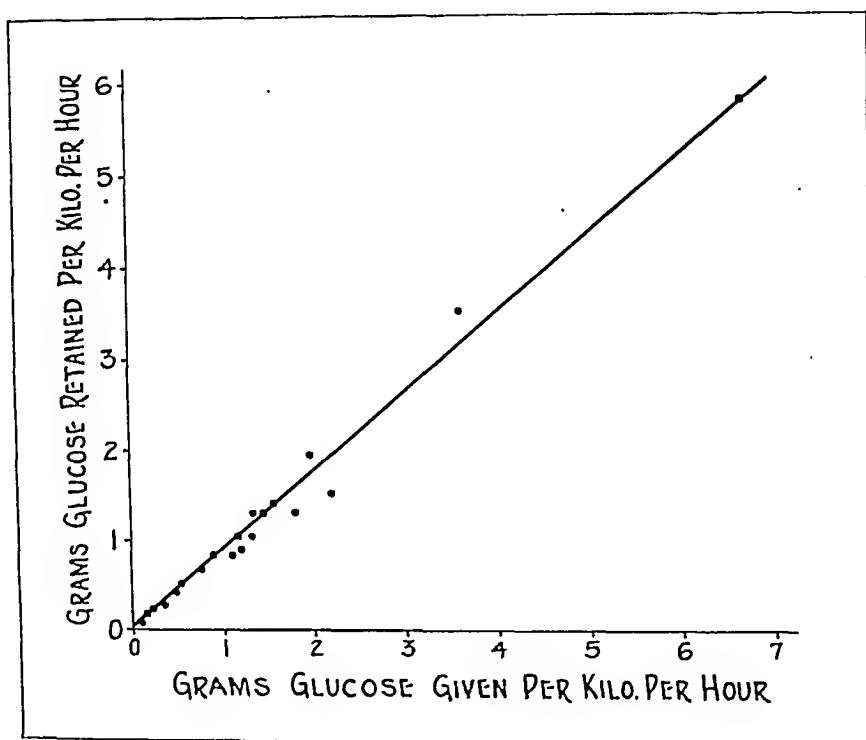


CHART 1.

before passage through liver and muscles. The occurrence of both small and large losses of glucose with both low and high rates of injection is interesting. The "spill" varied approximately from 0.3% to 30%, the average being 12.2%. For this we could find no explanation. The fasting blood sugar, the total amount of glucose given and the presence of fever were considered and found to be unrelated. Previous diet possibly had some effect, as glycosuria was slightly heavier in those who had fasted. This, however, was an inadequate explanation. From general knowledge of the many factors influencing carbohydrate tolerance, one might predict a wide variance in ill individuals in their ability to absorb glucose. In

addition to fever and previous diet, nervousness, temporary impairment of liver, pancreas, adrenals, thyroid and pituitary; the effect of such drugs as morphine, chloral, nembutal; acidosis; alkalosis; and inherited peculiarities, must effect sugar metabolism of the average surgical patient in varying degrees and combinations.

TABLE 1.—OBSERVATIONS ON THE INTRAVENOUS ADMINISTRATION OF GLUCOSE AT VARYING RATES TO HOSPITAL PATIENTS.

Case.	Diagnosis.	Weight (kilos).	Fasting blood sugar.	Fluid given.	Glucose given (gm.).	Glucose given (gm.), kilo/hr.	Glucose retained (gm.), kilo/hr.	Glucose lost, %.
1	Salpingitis	59	..	900 5%	45	0.073	0.072	0.533
2	Rupt. appendix	61.8	95	3500 5%	175	0.159	0.154	3.24
3	Rupt. gast. ulcer	61	107	4000 5%	200	0.222	0.217	1.5
4	Ac. appendix	80	90	2000 5%	100	0.390	0.290	27.20
5	Rupt. appendix	36	110	1000 5%	50	0.463	0.458	0.944
6	Uterine fibroid	80	91	3000 5%	150	0.512	0.500	2.39
7	Abortion	80	88	2000 5%	100	0.753	0.686	8.83
8	Ca. colon	54.6	115	1500 5%	75	0.926	0.832	10.00
9	Gang. appendix	86	103	2000 5%	100	1.13	0.82	27.34
10	Gast. neurosis	43	83	1000 10%	100	1.16	1.04	10.58
11	Pul. tuberc.	63.4	97	1000 10%	100	1.193	0.871	26.98
12	Ca. colon	54.5	115	1000 10%	100	1.301	1.065	18.32
13	Rupt. appendix	61.8	95	3000 5%	150	1.323	1.132	14.43
14	Rectal fistula	57	90	1000 5%	50	1.46	1.43	2.16
15	Rupt. appendix	63	83	1000 5%	50	1.59	1.44	0.22
16	Intest. obstruct.	41.8	130	3000 5%	150	1.824	1.307	28.33
17	Alcoholism	68	..	1000 10%	100	1.960	1.953	0.367
18	Intest. obstruct.	48.1	130	3000 5%	150	2.216	1.565	29.40
19	Chr. glomerulo-nephritis	73	92	500 20%	100	3.600	3.537	1.885
20	Sept. abortion	46	91	500 20%	100	6.620	5.773	12.83
21	Chr. glomerulo-nephrosis	73	92	50 50%	25	20.5	18.661	9.66
22	Ca. pancreas	59	105	3000 5%	150	0.880	0.370	58.00

These observations have a practical application. It is customary to administer glucose solutions at the arbitrarily determined rate of about 60 drops a minute. This limit is supposed to guard against embarrassment of the circulation, and to obviate appreciable wastage of glucose in the urine. At 60 drops per minute a liter of fluid requires 333 minutes for injection (20 drops = 1 cc.). At the rate of 0.85 gm. of glucose per kilo per hour, a liter of 5% solution requires 60 minutes for injection (16 cc. per minute), a liter of 10% solution, 120 minutes (8 cc. per minute). These rates, for volume, are approximately those recommended as safe by Gilligan and Alt-schule,³ 10 to 20 cc. per minute. The administration of 3 or 4 liters of fluid as commonly required to maintain fluid balance in fasting

and dehydrated adults consumes 15 to 20 hours at the 60-drop (3 cc.) per minute rate, five times as long as at 15 cc. per minute. It is our belief that the tedious drip method, often continued for 24 hours or longer, is needlessly tiresome and annoying to both patient and ward staff, and that practical considerations make it desirable to complete the parenteral administration of fluid during the daylight hours, as is possible in most cases. The studies of Gilligan and Altschule show this to be practicable, although due consideration must be given to circulatory weakness in individual cases, low plasma protein, weight of solution (5% glucose in physiologic saline is twice as heavy as either alone) and total volume to be injected. The present study shows that, although a portion of infused glucose is lost in the urine in all cases, this loss cannot be controlled by retarding the rate of infusion, and is, therefore, not an argument for drip administration.

Conclusions. The assimilation rate of intravenously administered glucose in hospital patients was found to be correlated with the rate of injection. The assimilation of 5.77 gm. per kilo of body weight per hour was observed.

In all cases some glucose was lost in the urine, the amounts varying from approximately 0.3% to 30% of the total given. The average loss was 12.2%.

The proportion of injected glucose lost in the urine was not correlated with the rate of injection, nor with the total amount given within the limits studied. This "spill" is conditioned by factors within the individual patients.

For practical purposes, the rate for the intravenous administration of glucose may be determined solely on two considerations: first, the hydrodynamics of the patient's circulation; second, technical convenience.

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FATAL HYPERINSULINISM WITH CEREBRAL LESIONS DUE TO PANCREATIC ADENOMA.

By A. J. KERWIN, M.D.,

LECTURER IN PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

(From the Department of Pathology and Bacteriology, University of Toronto and the Toronto General Hospital.)

ISLET cell tumors of the pancreas are rather uncommon in autopsy material. Some 11 examples have been encountered among 6700 autopsies in this department since 1925. Usually these were quite small and were picked up only on routine microscopic section of the pancreas. The true incidence is therefore probably much higher

than this would indicate. Commonly they give rise to no symptoms, because either they do not secrete insulin, or, if they do, there is insufficient to upset the normal carbohydrate regulating mechanism. Approximately 100 cases have been described in the literature.⁴ Four cases with surgical cure have previously been reported from this institution.³

The various symptoms resulting from hyperinsulinism are fairly well recognized and need not be recapitulated here. Wilder⁷ has recently discussed them in detail.

The present case was thought worthy of record because of the rapid course to a fatal outcome, and the fact that the proper diagnosis was made and then discarded because glucose therapy did not afford the expected relief.

Case Report. N. D., a married woman, aged 42. Except for an unusual number of headaches in the previous 4 months, she was well until August 3, 1940, when she became mentally confused and wandered aimlessly about the house. She recovered spontaneously but the next morning remained in bed in a stuporous condition despite the fact that she was expecting guests for dinner. By 10 A.M. she had become perfectly normal again without treatment. The following day she was given a complete physical examination, but nothing abnormal was found. For some months she had been taking thyroid extract for obesity without her doctor's knowledge. In the next week she had two more spells of amnesia and confusion which passed off apparently without treatment; an adequate history of these was lacking.

On the morning of August 9, she was found lying in bed in a comatose condition from which she did not recover all day. Examination that evening by a consultant revealed only right lower facial weakness; the reflexes were normal and there was no papilledema. During the examination, she roused herself somewhat and it was noted that her speech was thick and blurred; all test objects were called by the same name. Because of strong resistance on the part of the patient an attempt at lumbar puncture was unsuccessful. A few minutes after the struggle, she suddenly regained all her faculties and was apparently normal. Later in the week she had several similar attacks during which she was incontinent; the complete history of this period was not available.

On August 13, 1940, she was admitted to the hospital after having been in a deep coma for the previous day and a half. Physical examination except for the coma and absence of all reflexes was negative. There was no response to any stimuli. The temperature was 103° F. and the pulse rate 108 per minute and regular. The spinal fluid was normal to routine examination; the blood N.P.N. measured 58 mg. per 100 cc.

A provisional diagnosis of hypoglycemia was made. The blood sugar at 3 P.M. equaled 43 mg. per 100 cc. After this was reported, she was given 100 cc. of 50% glucose in addition to the continuous intravenous of 5% glucose she had already been receiving. At 9 P.M. the clinical condition was not improved in spite of the fact that the blood sugar had risen to 172 mg. The next morning her temperature had fallen slightly but she was still deeply unconscious; the blood sugar had dropped to 66 mg.; 100 cc. of 50% glucose was again administered intravenously, but the coma continued and the blood sugar that evening was only 42 mg. On August 15 the temperature had risen to 104°, the blood sugar was 40 mg., and her clinical condition was unchanged. After several previously unsuccessful

attempts, a duodenal tube was passed and feedings given. The blood sugar had risen that evening to 93 mg. per 100 cc., but she was unimproved.

Up to this time the diagnosis of pancreatic adenoma with hyperinsulinism had been considered likely, but in view of the failure of intravenous glucose to rouse her from coma, though the blood sugar had been brought to normal or over on two occasions, this diagnosis was abandoned. It was thought that she might be suffering from an unusual form of encephalitis.

On August 17 the spinal fluid sugar was 73 mg. per 100 cc. Her condition remained unchanged until August 19 when the temperature rose to 106°, the pulse to 140 and she died 16 days after the beginning of the present illness and after 8 days of continuous coma.

Autopsy findings (complete autopsy 1½ hours after death). Gross: The body was well developed and rather obese, weighing 162 pounds. The only findings of interest were in the pancreas and the brain.

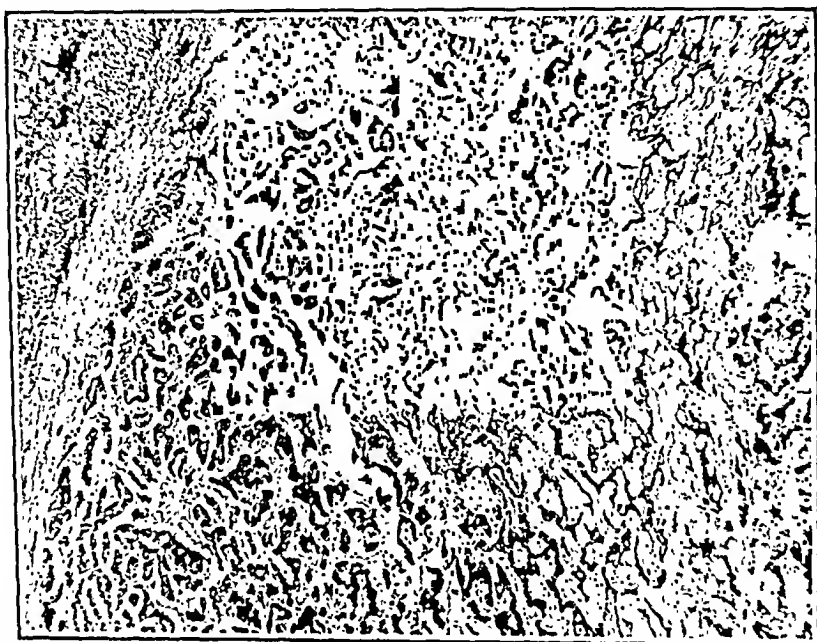


FIG. 1.—Larger islet cell adenoma of pancreas, including part of capsule and showing fibrosis of central portion. $\times 25$. H. & E. (Low power.)

The pancreas weighed 65 gm. and measured 18 cm. in length. The configuration was normal except that in the tail, 3 cm. from the end, there was a small spherical nodule. About one-half of this mass protruded from the middle of the anterior surface of the pancreas. It was soft, well encapsulated and was dissected out easily; it weighed 2.7 gm. and measured 1.9 cm. in diameter. The cut surface was uniformly yellowish-white and not congested. Serial section of the rest of the pancreas revealed no lesions.

Assay of the insulin content of this tumor (Dr. D. A. Scott, of the Connaught Laboratories), showed 30 units of insulin per gm., or approximately 10 to 15 times the content of normal pancreatic tissue.

The brain weighed 1325 gm. There was congestion of the superior cerebral veins and a small quantity of fresh blood in the subarachnoid space over the right frontal lobe. The external surface showed no cortical atrophy or other abnormality. Section of the brain revealed some edema with narrowing of the ventricles but no other changes.

The pituitary weighed 0.6 gm. and was grossly normal.

The other organs were remarkably free from lesions.

Microscopic: Pancreas—the tumor was composed of epithelial cells arranged in slender ribbons, rounded masses and alveolar structures (Fig. 1). The arrangement varied in different fields but was chiefly of the ribbon type; often these ribbons were made up of a single layer of cells, but many also resembled pseudostratified columnar epithelium. The alveolar structures consisted of a single row of columnar cells around a capillary, only occasionally forming a complete circle. It is possible that these differences in appearance were due to the cutting of very tortuous ribbons at various levels and in different directions.

With hematoxylin and eosin stain some of the epithelial cells had large round nuclei which tended to be vesicular in type, but most of them were smaller and oval in shape and the chromatin was more diffusely distributed (Fig. 2). Usually the nuclei were centrally placed; the oval nuclei were often squeezed slightly to one pole by the pressure of contiguous cells. In the alveolar structures the nuclei were nearly always peripheral. In gen-

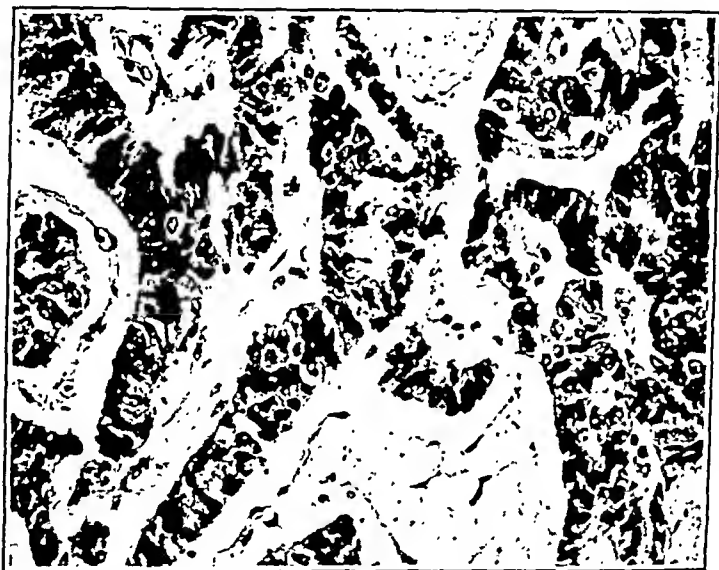


FIG. 2.—Larger adenoma to show cellular structure. $\times 240$. H & E. (High power.)

eral appearance most of these cells did not closely resemble normal islet cells, but near the capsule some did, the nuclei being smaller and more diffusely stained. Mitotic figures were rare and there was no invasion of vessels. The cytoplasm was finely granular and purplish in color.

Surrounding these columns of cells but separated from them by an open space was a fine supporting network of naked capillaries usually having a diameter about that of a red cell. In many places there appeared to be openings in these capillaries and a number of red cells lay free in the spaces next to the epithelial masses. Near the capsule the framework was thicker and there were fibrocytes surrounding the capillaries; a number of lymphocytes were also seen. Toward the center of the tumor the cell cords were separated and compressed by irregular and relatively acellular masses of connective tissue surrounding the capillary network. In a few areas these showed beginning hyalinization; no calcification was evident. The occasional small pancreatic duct radicle was observed.

The capsule of the tumor was composed of a layer of collagenous connective tissue of variable thickness in which lay a number of islets and small ducts. These islets were somewhat flattened but appeared normal except that some were several times the usual size.

Though special stains of the formalin-fixed tissue were not entirely satisfactory, Bowie's stain did show that about 75% of the granules appeared to be of the beta type. Most cells contained only beta granules; many contained alpha granules as well.

Routine blocks of the pancreas elsewhere revealed another small adenoma about half the size of a low power field (Fig. 3). The general structure was the same as that of the larger tumor except that the capsule was thin and in some areas deficient, and there was much less fibrosis.



FIG. 3.—Smaller adenoma showing resemblance to the larger one. $\times 70$. H. & E. (Low power.)

Several other sections of the pancreas presented no abnormality.

Brain. Numerous blocks were cut and stained with hematoxylin and eosin, cresyl violet, Mallory's phosphotungstic acid and Mallory's connective tissue stain.

In the left frontal lobe there was much thickening and gliosis of the molecular cortical layer. Edema was well marked in both the gray and white matter and there was considerable swelling of oligodendroglia. The small vessels were congested and there was hemorrhage into the perivascular spaces in some areas; in others a few lymphocytes were seen. Some of the cortical nerve cells showed pyknosis and shrinkage. In the deeper layers of the cortex neuronophagia was evident. In the other sections of the cerebrum, similar changes were present in varying proportions. The left hypothalamus presented subependymal gliosis, congestion and an occasional perivascular hemorrhage; no significant nerve cell changes were noted.

In the midbrain there was moderate subependymal gliosis below the aqueduct and just deep to the pia. Edema and congestion were evident here also and there was some swelling and chromatolysis in the nerve cells of the oculomotor nucleus.

In the pons the ependyma was thrown into folds by proliferation of underlying glial tissue; gliosis was also evident around the small vessels. Many of the nerve cells revealed acute degenerative changes with swelling of the cell bodies and eccentrication of the nuclei.

Transverse section of the open medulla showed an intact ependyma beneath which lay a narrow band of gliosis. Edema and congestion were evident throughout the tissue. In the superficial portions of the floor of the fourth ventricle a few of the nerve cells showed pyknosis but the majority were entirely normal.

The arteries and arterioles were everywhere normal.

Pituitary. The gland was preserved in formol-saline and cut transversely. Sixteen pairs of slides were made at various levels and stained with hematoxylin and eosin and Mann's stain. There was some variation in the picture from section to section. The normal proportions of the various cell types were present in several sections, but on the whole the eosinophils were less numerous than usual. The number of chromophobes was definitely increased in many places. The basophils were slightly increased in some sections but this was not a prominent feature. No basophil adenomata were seen; two small, poorly circumscribed, nodular masses of chromophobe cells were identified. The pars intermedia presented no abnormality. Slight invasion of the posterior lobe by basophils was evident in some sections but this never exceeded normal limits.

Microscopic examination of the *other organs* revealed no abnormalities.

Comment. The majority of cases of islet cell tumor run a prolonged intermittent course which may last for some years. One case, reported by Barnard,² died about 4 months after the onset of symptoms, but I have not encountered in the literature a case comparable to this in which the total length of the illness was apparently only 16 days.

In this patient stupor and mental confusion were the outstanding features, and the attacks came on without the prodromal symptoms and signs so frequently seen. The severity of the process probably accounted for this. Motor phenomena except for facial weakness on one occasion and speech defect were notably absent.

One attack terminated spontaneously just after a struggle induced by attempted lumbar puncture. One may postulate that the physical effort resulted in release of adrenalin with mobilization of glucose from the liver.

Wilder,⁷ quoting Whipple, states that the relief of symptoms and return to normal resulting from the administration of glucose is one of the criteria for the diagnosis of hyperinsulinism. Usually this criterion can be fulfilled, but unfortunately in the present case the strict application of this principle caused the abandonment of the correct diagnosis. The effect of glucose is generally dramatic, but if the attack is very severe and prolonged no clinical improvement may result.

In the temporary episodes quickly and completely relieved by glucose, it seems not unlikely that the hypoglycemia is *per se* responsible for the symptoms, as it apparently is in hypoglycemia from causes other than hyperinsulinism. In the severe attacks whose sequelæ may be hemiplegia, idiocy, dementia, and so on, and

in which bringing the blood sugar to or above normal does not restore the patient, cerebral damage is probably the main factor.

The cerebral changes produced by fatal hyperinsulinism whether due to islet cell tumor or insulin shock therapy are variable. They have recently been reviewed by Malamud and Grosh,⁶ and Baker.¹ Congestion, edema, hemorrhages, perivascular lymphocytic infiltration, cortical atrophy, degeneration of ganglion cells in cortex and basal ganglia, degeneration of neurones and encephalomalacia have been described by different authors. Similar lesions have been produced in the experimental animal in some cases.

In this case, moderate edema and congestion, and a small sub-arachnoid hemorrhage were present in the gross. Microscopically, the cerebral cortex showed some degeneration of nerve cells and neuronophagia. Nerve cell changes were also seen in the mid-brain and pons but not in the hypothalamus. The rapid progress of the disease would seem to account for the lack of striking changes in the brain. The gliosis, though not marked, is difficult to explain. It is unlikely that it could have developed in just over 2 weeks. Nor is it probable that it represents pre-senile changes in so young a woman, especially in view of the complete absence of vascular sclerosis. An alternative explanation is that the patient suffered a number of mild hypoglycemic attacks which passed unnoticed. It cannot be denied for certain that the headaches over a period of 4 months preceding the apparent onset of the illness did not represent hypoglycemic episodes; if they did, they would seem to have been too slight to cause cerebral damage.

The mechanism of insulin action on brain tissue has not been satisfactorily explained. A number of theories have been advanced, but no adequate evidence for any of them has been adduced.

Several authors have drawn attention to changes in the pituitary gland. Friedman⁶ has recently described basophil and eosinophil hyperplasia of the anterior lobe in 2 cases, 1 of which also showed massive basophil invasion of the posterior lobe. Malamud and Grosh⁶ mentioned in their case that there was eosinophil hyperplasia of the anterior lobe and a small basophil adenoma. No alterations of the pituitary have been consistently described and, in most cases, the gland has been normal. Those changes present in this case were not of marked degree and did not correspond to those noted by Friedman. Their significance, if any, is not clear.

Summary. A case of fatal hyperinsulinism due to multiple islet cell tumors of the pancreas has been reported. The patient died 16 days after the onset of the first symptoms, and after 8 days of continuous coma.

The tumor contained 30 units of insulin per gram of tissue.

The brain showed congestion, edema, hemorrhages, nerve cell degeneration and gliosis, but these changes were not severe.

The case was notable on account of the rapidly fatal issue and the

fact that the diagnosis was missed because the patient did not respond to the administration of glucose.

I am indebted to Prof. William Boyd for permission to publish this case and to Prof. Eric Linell for the use of his reports on the brain and help in their interpretation.

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THE PROGNOSIS OF PNEUMOCOCCIC MENINGITIS TREATED WITH CHEMOTHERAPY.

BY G. HOLLANDER, M.D.,

INTERN, JEFFERSON MEDICAL COLLEGE HOSPITAL, PHILADELPHIA, PA.; FORMERLY
INTERN IN PHYSIOLOGICAL CHEMISTRY.

(From the Department of Pediatrics, Jefferson Medical College Hospital.)

WITH the growth, popularity and intelligent use of the newer methods of therapy in pneumococcic meningitis the prognosis has been much improved. Following our first successful recovery of a Type XIV pneumococcic meningitis we became sufficiently interested to review the literature in order to determine the value of chemotherapy in this infection. This report is a review of the 260 reported cases that have been treated with chemotherapy, with or without specific serum, in an attempt to evaluate the effectiveness of each of the therapeutic agents, alone and combined.

TABLE 1.—RESULTS OF TREATMENT OF PNEUMOCOCCIC MENINGITIS IN ALL REPORTED CASES.

	Total.	Died.		Recovered.	
		No.	%.	No.	%.
Sulfanilamide	78	50	64.1	28	35.9
Sulfanilamide—serum	50	34	68.0	16	32.0
Sulfapyridine	82	34	41.5	48	58.5
Sulfapyridine—serum	50	21	42.0	29	58.0
Chemotherapy	160	84	52.5	76	47.5
Total	260	139	53.5	121	46.5

Chemotherapy. In the years previous to the use of the sulfonamide drugs the number of cures (63) were so few that the fatal prognosis in this disease was considered to be from 95% to 100%. From Table 1 it is seen that in 160 cases treated with chemotherapy alone, sulfapyridine bears out experimental evidence that it is a more efficacious drug in pneumococcic meningitis than is sulfanilamide. In 82 cases treated with sulfapyridine there were 58.5% recoveries compared to the recovery rate of 35.9% in 78 cases treated with sulfanilamide.

Other sulfonamide drugs have to be considered as possible therapeutic agents. While a recovery with the use of sulfathiazole has been reported²⁵ its poor concentration in the spinal fluid compared to its concentration in the blood eliminates it as a factor in the treatment of this infection. Sulfadiazine (2-sulfanilamidopyrimidine) has been shown to pass over into the cerebrospinal fluid^{22,23} in concentrations of two-thirds to four-fifths of that which exist in the blood. While experimentally¹² it is less effective in Type I pneumococcal infections in mice, clinical evidence may show it to be of some value in this disease.

Chemotherapy and Specific Serum. It has been definitely stated by many that there exists no clear evidence that the use of serum with the sulfonamide drugs has materially affected the course of pneumococcal infections.^{3,10,17,19,29} Others^{2,4,5,7,15} have found both experimentally and clinically that the efficiency of specific serum as well of the sulfonamide drugs, was enhanced by the use of the two simultaneously. In these studies this action was beyond that which would be expected from the simple additive effect of the two.

Table 1 shows that the percentage of recovery with sulfapyridine as compared to sulfapyridine-serum therapy is similar, 58% recoveries. In Types I, V, and VII in which the value of serum is the most efficacious, Table 2 shows that there is little difference in the fatality rates from drug or drug-serum therapy with the exception of Type V, in which combined therapy is of value (83% recovery with sulfapyridine-serum therapy). However, combined sulfapyridine-serum therapy may raise the prognosis in the younger age groups (Table 4), and in meningitis secondary to an otorhinologic condition (Table 3).

It has been suggested that both specific serum and sulfapyridine be administered in adequate dosage as early as possible for its immediate effect in tiding the patient over the immediate emergency since Haviland⁹ has shown that with chemotherapy alone antibodies may not occur for several days after the temperature has fallen to normal, while MacIntosh and Whitby¹³ demonstrated that it takes 6 hours or more for the bacteriostatic action of sulfapyridine to take place. Contrary to this, Spring and his associates²⁶ demonstrated that in some patients even the presence of a high titer of antibodies does not guarantee recovery, while recovery may occur in others without demonstrable antibodies in the blood stream. Furthermore the combined drug-serum therapy may be given to the younger age groups, in meningitis secondary to an otorhinologic condition, in patients who have an idiosyncrasy to the sulfonamides in an effort to lessen toxic effects, in those who fail to respond within 24 to 48 hours to chemotherapy and in those cases in which the pneumococcus develops a tolerance to the drug.

Dosage. The doses of the sulfonamide given to recovered cases has been quite variable. MacKeith¹⁴ has reported a recovery with

a total dose of 12 gm. of sulfapyridine while Rhoads²⁴ has had to use a dose as high as 176 gm. throughout the illness for recovery to occur. Fatal cases have received doses as high as 90 gm. without appreciable effect.

TABLE 2.—TYPES OF PNEUMOCOCCUS IN REPORTED CASES OF PNEUMOCOCCIC MENINGITIS WITH THE USE OF SULFONAMIDE DRUGS.

Type.	Sulfanilamide.		Sulfanilamide serum.		Sulfapyridine.		Sulfapyridine serum.	
	Died.	Recovered.	Died.	Recovered.	Died.	Recovered.	Died.	Recovered.
I	3	2	0	2	1	3	2	3
II	0	0	0	2	0	0	0	0
III	10	8	3	1	4	4	3	6
IV	2	2	0	1	1	3	3	3
V	1	3	0	0	0	3	1	5
VI	3	0	1	2	3	0	0	0
VII	3	0	0	4	0	0	1	0
VIII	0	0	1	0	0	0	1	0
IX	1	0	0	0	0	1	1	0
X	0	0	0	0	3	1	1	1
XI	0	0	1	0	0	0	0	0
XII	0	1	0	0	1	1	0	0
XIII	1	1	0	0	0	0	0	1
XIV	0	1	0	0	2	2	2	3
XV	0	1	0	0	0	1	0	0
XVI	0	0	0	0	1	0	0	0
XVII	0	1	0	1	1	1	0	2
XVIII	1	0	2	0	4	2	3	0
XIX	1	0	0	1	2	2	0	2
XX	0	1	0	0	0	0	0	1
XXI	0	0	1	0	0	0	1	1
XXII	0	0	0	0	1	0	1	0
XXIII	0	0	0	0	1	2	1	0
XXIV	0	0	0	0	0	0	0	0
XXV	0	0	1	0	0	2	0	0
XXVI	0	0	0	0	0	0	0	0
XXVII	0	1	0	0	1	0	0	0
XXVIII	0	1	1	1	0	1	0	0
XXIX	0	2	0	0	0	0	0	0
XXX	0	0	0	0	0	0	0	0
XXXI	0	1	0	1	1	0	0	0
XXXII	0	0	0	0	0	0	0	1
Over XXXII	2	0	0	0	1	1	0	0
Not stated	22	2	23	0	6	18	0	0
Total	50	28	34	16	34	48	21	29

The difficulty in regard to dosage is the irregularity of absorption of the drug, thus accounting for the great variations in its effect and in its concentrations in both blood and spinal fluid. In this respect while a level of sulfapyridine ranging from 10 to 20 mg. per 100 cc. of blood is desirable, Hodes¹¹ has reported recoveries with blood levels as low as 1.7 mg. per 100 cc. in some, to as high as 30.3 mg. per 100 cc. in others; with spinal fluid levels ranging from 1.1 mg. per 100 cc., to as high as 29 mg. per 100 cc.

The time required for the cerebrospinal fluid to become sterile varies considerably both in regard to the concentration of the drug and the dosage. Generally in the majority of recovered cases it

becomes sterile in 4 days or less. A sterile culture obtained within this time was only rarely followed by death. In those cases with relapse, during which time the cerebrospinal fluid again contained pneumococci, the time taken to sterilize the spinal fluid also varied, but averaged about 7 days.

TABLE 3.—ETIOLOGIC INCIDENCE OF REPORTED CASES OF PNEUMOCOCCIC MENINGITIS WITH RECOVERY COMPARED TO INCIDENCE OF TOTAL REPORTED CASES.

	Ay.* inci- dence.	Non- specific treat- ment.	Specific serum.	Sulfanil- amide.	Sulfanil- amide and serum.	Sulfapyr- idine.	Sulfapyr- idine and serum.
Otitis media and/or mastoiditis	101 34.8%	8 28.5%	1 2.9%	15 53.6%	3 18.8%	14 29.2%	14 48.1%
Sinusitis	14 4.8%	1 3.6%	0	3 10.7%	3 18.8%	3 6.2%	1 3.5%
Head injuries	22 7.5%	1 3.6%	6 17.1%	2 7.1%	1 6.2%	1 2.1%	1 3.5%
Operations on head	8 2.7%	1 3.6%	1 2.9%	3 10.7%	0	2 4.2%	1 3.5%
Pneumonia	49 16.9%	5 17.9%	9 25.8%	0	1 6.2%	3 6.2%	2 6.9%
Upper respiratory infections	18 6.2%	5 17.9%	6 17.1%	1 3.6%	0	2 4.2%	2 6.9%
Primary	65 22.3%	6 21.3%	12 34.2%	3 10.7%	8 50.0%	15 31.3%	7 24.1%
Miscellaneous	14 4.8%	1 3.6%	0	1 3.6%	0	8 16.6%	1 3.5%
Total	291	28	35	28	16	48	29

* Total cases of authors quoted.^{6,8,20,21,24,27}

Type of Pneumococcus. Investigation with regard to the types of pneumococci which are involved in pneumococcic meningitis, as given in Table 2, show the wide variety which are responsible in this infection. The effect of the sulfonamides upon the various types shows that their efficiency is relatively unimpaired by the type of pneumococcus involved. This is in accordance with the experimental work of Whitby²⁸ and Maclean¹⁵ who have both shown that while pneumococci vary enormously in their sensitivity to the sulfonamides, the variation depends not on the type but on the individual strain. With the exception of Types III and V pneumococcic meningitis, there is little correlation, at least at present, between the types of pneumococci and whether sulfonamides alone or combined with serum are used. In these two types the combined sulfapyridine-serum therapy seems to be indicated.

Etiology. Pneumococcic meningitis occurs as a secondary complication in a number of disorders, including middle-ear or mastoid disease, pneumonia, paranasal sinusitis, upper respiratory infections, endocarditis, brain abscess, pneumococcic peritonitis and pleuritis. It most frequently occurs secondary to an otorhinologic condition, 34.8% of all cases, followed next in frequency by the primary involvement of the meninges, shown in Table 3 to occur in 22.3%.

In the 184 recoveries given in Table 3 the incidence of spontaneous

recoveries closely follows its occurrence as a whole. Serum therapy shows poor results in meningitis secondary to otorhinologic conditions, possibly due to the fact that there was inadequate treatment of the primary focus. This is very much offset by the use of chemotherapy, where with drug alone or drug-serum therapy there is approximately 50% recovery.

TABLE 4.—AGE INCIDENCE IN CURED CASES OF PNEUMOCOCCIC MENINGITIS IN COMPARISON TO AVERAGE INCIDENCE.

Age.	Incidence.*	Non-specific therapy.	Serum.	Sulfanilamide.	Sulfanilamide and serum.	Sulfapyridine.	Sulfapyridine and serum.
Up to 1 yr.	33 14.1%	4 13.8%	0	0	0	0	3 10.3%
1 to 5 yrs.	44 18.7%	6 20.7%	3 8.6%	5 17.9%	0	1 2.1%	4 13.8%
5 to 10 yrs.	33 14.1%	5 17.2%	5 14.3%	6 21.4%	4 25.0%	8 16.5%	4 13.8%
10 to 20 yrs.	29 12.3%	6 20.7%	8 22.9%	8 28.6%	8 50.0%	9 18.8%	9 31.0%
Over 20 yrs.	90 38.3%	8 27.6%	18 51.4%	7 25.0%	4 25.0%	23 47.9%	7 24.2%
Not given	6 2.5%	0	1 2.8%	2 7.1%	0	7 14.6%	2 6.9%
Total cases	235	29	35	28	16	48	29

* As given by Neal.¹⁵

PROTOCOL.—CASES TREATED AT JEFFERSON HOSPITAL WITH CHEMOTHERAPY.

Sex.	Age.	Type of pneumococcus.	Source of infection.	Treatment.	Remarks.
F	56	*	Primary	Spinal taps; sulfanilamide; azosulfamide	Diabetic patient with diabetes under control; died 24 hrs. after admission.
M	6 mos.	VI	Primary	Spinal taps; sulfanilamide	Died 6 days after admission; spinal fluid never sterile.
F	18 mos.	IX	Pneumonia	Spinal taps; azosulfamide; optochin	Patient died on 8th day; pneumonia.
M	6 mos.	VI	Pneumonia	Sulfapyridine	mission.
M	8	III	Otitis media	Spinal taps; sulfapyridine (orally, I.V.)	No signs of meningitis 1 mo. after admission; relapsed in 6 wks. and died; brain abscess on autopsy.
M	5	XIV	Primary	Specific serum; sulfapyridine (oral, subcut., I.V.)	Spinal fluid sterile on 3d day; patient recovered.
M	38	XVIII	Primary	Spinal taps; specific serum; sulfapyridine	Patient died on 4th day; spinal fluid culture positive.
M	21	X	Foll. skull fracture	Spinal taps; specific serum; sulfapyridine	No signs of meningitis 6 wks. after admission; relapsed, died in 3 days.
F	2 mos.	V	Otitis media	Sulfathiazole	Patient died within 24 hrs. of admission.

* Type not determined.

The poorer prognosis shown in pneumococcic meningitis arising secondary to pneumonia is worth noting. It has already been shown^{15,24} experimentally that there occurs an acquired tolerance of the pneumococci to sulfapyridine. This has been shown clinically by May¹⁶ and by Anger¹ who with pneumococci cultured from the spinal fluid of a case of pneumococcic meningitis showed that the strain of pneumococcus cultured from the spinal fluid before treatment was sensitive to sulfapyridine while the same strain cultured

from the fluid after 29 days of intensive treatment showed itself to be resistant to sulfapyridine. A further possibility is that in those pneumonia patients in whom the organism becomes resistant to sulfapyridine and the disease spreads to involve the meninges the prognosis is poor and here combined drug-serum therapy should be used.

Age. While pneumococcus meningitis occurs in all age groups, Table 4 shows it to occur more frequently in children. Most of the recoveries obtained with specific serum have occurred in adults, while the use of chemotherapy and still better sulfapyridine and serum combined give a better prognosis for cure in the younger age groups. This combination gives the best prognosis in the ages between 10 and 20 years in which almost one-third of the recoveries have occurred.

Summary and Conclusions. 1. The clinical results obtained in the treatment of 160 reported cases of pneumococcic meningitis with chemotherapy bear out experimental results that sulfapyridine is the drug of choice in the treatment of this infection.

2. At present there is no clear evidence that the additional use of specific serum with sulfapyridine should be a routine procedure. The percentage of recovery with sulfapyridine alone is approximately that of combined sulfapyridine-serum therapy. The combination is indicated in the treatment of Type III and V pneumococcic meningitis, in those infections secondary to an otorhinologic condition and to pneumonia, and in the younger age groups.

3. No definite correlation could be made between the dose of the sulfonamide drug used, its concentrations in both blood and spinal fluid and the clinical response.

4. The prognosis is favorable if the cerebrospinal fluid has been sterilized within 4 days with the use of sulfapyridine.

5. Almost every type of pneumococcus has been cultured from cases of pneumococcic meningitis. With the exception of Types III and V, there is little correlation between the type of pneumococcus and the prognosis.

6. The prognosis in pneumococcic meningitis secondary to pneumonia is poor, possibly due to an acquired tolerance of the invading organism to the sulfonamide drug.

7. The prognosis in the younger age groups is improved with the use of combined drug-serum therapy, with the best prognosis occurring in the ages from 10 to 20 years.

8. In 9 cases of pneumococcic meningitis treated at Jefferson Hospital with chemotherapy, only 1 recovered. Two other cases, Types III and X, had apparently recovered but died following unsuccessful treatment of a relapse. The recovered case received combined sulfapyridine-serum therapy.

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PNEUMOCOCCAL CAPSULAR POLYSACCHARIDE AND ANTI-BODY IN PLEURAL EXUDATES.*

BY PAUL F. DE GARA, M.D.,†

DAZIAN FELLOW,

JESSE G. M. BULLOWA, M.D.,

CLINICAL PROFESSOR OF MEDICINE, NEW YORK UNIVERSITY COLLEGE OF MEDICINE;
VISITING PHYSICIAN, HARLEM HOSPITAL,

AND

SAMUEL C. BUKANTZ, M.D.,

LITTAUER FELLOW IN PNEUMONIA RESEARCH,
NEW YORK, N. Y.

(From the Medical Service, Harlem Hospital, Department of Hospitals, New York City, and the Littauer Pneumonia Research Fund of New York University College of Medicine.)

STUDIES on the diagnostic and prognostic significance of the detection of pneumococcal capsular polysaccharide ("SSS") in blood and urine of patients with pneumococcal pneumonias have been reported.^{1,3,4,8,9a,b} We record in this study from the Pneumonia Service at Harlem Hospital during the season of 1939-40 the occurrence of SSS, and of agglutinative and precipitative antibodies in pleural exudates.

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† Present address: Cornell University Medical College.

An extensive bacteriologic study of pleural effusions was first published about 50 years ago, by Netter,¹⁶ and more recently, in 1930, by Locke¹⁵ who showed that pneumococcus I was the most frequent cause of empyemas.

Studies on antibodies in pleural effusions were made by Griffon in 1899.¹³ He found that pneumococci grown in a pneumococcic pleural exudate might become agglutinated. Cole,⁵ in 1917, found that pleural empyema fluids inhibited the protective power of homologous antipneumococcal sera, and did not contain agglutinins or protective substances. More recently, in 1932, Finland¹⁰ published immunologic studies on 31 specimens of pleural fluid from 19 patients with typical lobar pneumonias. He found SSS only in infected fluids and antibodies only in sterile fluids.

Several other immunologic studies concerning the bactericidal properties of pleural exudates have been made.^{6a,7,11,12,17-22} In these studies all the fluids accompanied by pleural inflammation were bactericidal for the organisms tested, including the pneumococcus.

In the present series pleural exudates of patients with typical lobar pneumonias were examined bacteriologically and immunologically (detection of SSS, agglutinins and precipitins) and the findings correlated with other bacteriologic, immunologic and clinical data.

An attempt was made to determine the pneumococcic type responsible for an illness by identifying with pooled serums the specific capsular polysaccharide in the pleural exudate.

The "optimal" concentration of antibody required for the detection of SSS in pleural exudates was determined for some pneumococcic types.

Material and Methods. A total of 44 specimens of pleural exudate from 27 patients with lobar pneumonias were examined. Forty-three samples from 26 patients were due to pneumococci; one exudate was obtained from a patient suffering from a *Bacillus Friedlander A* pneumonia. For controls, 4 pleural fluids (from 4 patients) with diseases other than pneumonia were studied. Venous blood and urines were examined in some of the patients.

Detection of Capsular Polysaccharide* in Pleural Exudates. The method of determining capsular polysaccharide by type-specific or by pooled sera, and the method of determining antibodies have been already described in previous publications^{2,3,6b} in studies with blood and urine.

One-half milliliter of the undiluted clear supernate, obtained by centrifugation, of the pleural fluid was mixed with 0.5 ml. of the homologous rabbit antiserum in appropriate dilution; for controls 0.5-ml. portions of the same pleural fluid were mixed in a second and in a third tube with 0.5 ml. of a heterologous rabbit antiserum and with 0.5 ml. of saline respectively. The two controls always yielded negative results. In a few cases the undiluted supernate of the pleural fluid contained such large amounts of SSS that no reaction with the type-specific antiserum was observed. Precipitates appeared, however, when the tests were repeated with 1:2, 1:4, and 1:8 dilutions of the pleural exudate.

* The capsular polysaccharide and the serum used were those commercially available or supplied by the Lederle Laboratories, Inc., and were used in our previous studies.

TABLE 1.—BACTERIOLOGIC AND IMMUNOLOGIC STUDIES OF PLEURAL EXUDATE AND OTHER CLINICAL AND LABORATORY OBSERVATIONS.

Case No.	Type.	Age and sex.	Lobe involved.	Day of disease.				Serum treatment, units and kind.	Sulfapyridine, total gm.	Blood.				Pleural exudate.				Outcome.
				Serum. Started.	Thora- centesis.	Thora- centesis, Do- no.	Thora- centesis, eotomy.			Cul- ture.	SSS.	Agg.*	Prec.*	Cul- ture.	SSS.	Agg.*	Prec.*	
1	I	31 F	R.L.	..	0	30	39	...	66	0	0	64	0	+	++++B	0	0	Recovered
2	I	5 M	R.U.	..	6	37	43	..	20	0	+	++B	0	0	Recovered
3	I	35 M	R.M. R.L.	6	..	18	6	310,000 R	..	0	0	+	++++B	0	0	Recovered
4	II	60 M	L.L.	4	..	9	..	255,000 II	..	0	0	32	8	+	+	0	0	Recovered
5	III	56 M	L.L.	..	?	3h 9h 11h 15h 23h	18h	...	67	0	+	0	0	++++	++B ++B ++B ++B ++B	0 0 0 0 0	0	Died
6	IV	27 M	L.U. L.L.	3	..	3	..	253,000 R	...	+	+	++B	0	0	Died
7	V	32 F	R.L.	?	?	10h 11h 15h	21h	437,000 R	95	0	+++	++B ++B ++B	0 0 0	0	Recovered
8	V	58 M	L.L.	..	8	23	32	...	79	+	0	0	0	+	asP	0	0	Recovered
9	VI	30 F	R.L.	7	..	17 21	21	610,000 R	..	+	0	61	16	++	++B ++B	0 0	0	Recovered
10	VIII	45 M	L.L.	3	6	21	28	163,750 II and R	57	0	+	++B	0	0	Recovered
11	VIII	23 M	L.L.	1	4	11	13	177,750 R	23	+	0	+	++++B	0	0	Died
12	VIII	28 M	R.L.	6	1	7	..	290,000 R	30	+	0	61	16	+	++++B	0	0	Died
13	XIV	50 M	R.L.	..	9	35 40	43	...	87	+	0	64	8	++	++++B ++P	0 0	0	Recovered

14	B. Fried- lander A	37	M	L.L.		3	13		...	64	0	0	0	S	+	+++	+	0	Recovered
15	II	24	F	L.L. R.L.	4	4	12 60	..	535,000 H and R	28	+	0	64	16	0	0	0	0	Recovered
16	III	47	M	R.L. R.U.	3	3	9 10 12 14	17	332,500 R	57	0	+	32	16	0	0	0	0	Died
17	III	49	M	R.U.	..	3	9	25	0	0	4	0	0	0	0	0	Died
18	VII	39	M	R.U.	5	..	18	..	322,000 R	...	+	0	0	0	0	0	Recovered
19	II	58	M	L.L. R.L.	10	8	7	..	518,000 R	44	+	0	0	0	0	0	Recovered
20	VIII	43	M	R.L. R.M. ?	1	1	10	..	186,400 H	14	+	+	64	16	0	0	0	0	Recovered
21	XII	30	F	R.L.	..	6	16	17	0	0	0	0	0	Recovered
22	III	43	M	L.L.	2	2	12	..	300,000 R	21	0	0	0	0	0	0	0	0	Recovered
23	XXIX	29	F	L.L.	..	?	5h	132	0	0	0	0	0	Died
24	XIII	26	F	R.L.	15	15	13 24 30 43	..	625,000 R	18	0	0	16	16	0	0	0	4	Recovered
25	V and VIII	53	M	L.L.	4	12	14	..	237,000 R (VII) 280,000 R (V)	22	0	0	0	16 (V)	0	Recovered
26	I	26	F	L.L.	..	3	18 19	32	0	0	0	0	8 4	0	Recovered
27	I	61	M	R.U.	13	3	14 15	..	381,500 R	67	+	0	0	8 4	0	Died

h, day of hospitalization (? day of disease); P, precipitate; B, button; H, horse serum; R, rabbit serum.

* The figures given for agglutination and precipitation indicate the highest final dilution of the material under investigation (blood, pleural exudate) where positive reactions were observed.

Detection of Agglutinins. One-half-milliliter quantities of serial dilutions, carried to $\frac{1}{32}$, of the supernate of the pleural exudate, were mixed with 0.5 ml. of the saline suspension of heat-killed homologous pneumococci.

Detection of Precipitins. One-half-milliliter quantities of serial dilutions, carried to $\frac{1}{8}$, of the supernate of the pleural exudate, were mixed with 0.5 ml. of an appropriate dilution of homologous SSS. A control tube, containing 0.5 ml. of the pleural exudate with 0.5 ml. of a heterologous SSS solution was negative in all the experiments. The tests were always made in 10 by 75 mm. Pyrex tubes by the centrifugation method² at 2000 r.p.m. for 30 minutes. Positive results varied from a cloud ("+") to a precipitation or button formation of varying intensity ("±p" to "++++B").*

Controls. Further controls included the following mixtures: 1, type-specific serum plus type-specific SSS; 2, type-specific serum plus saline; 3, heterologous serum plus its type-specific SSS; 4, heterologous SSS plus saline; 5, homologous SSS plus saline; 6, heterologous SSS plus saline; 7, type-specific serum plus bacterial suspension; and 8, saline plus bacterial suspension. The controls always yielded the expected results (positive in tubes Nos. 1, 3 and 7; negative in Nos. 2, 4, 5, 6 and 8).

Results. The results of the bacteriologic and immunologic studies of the pleural exudates, and other clinical and laboratory observations are recorded in Table 1. The 44 samples of pleural fluid from 27 patients may be divided into three groups. The first group of 28 fluids (Patients 1 to 16) includes those having no antibody but containing pneumococci and SSS either on the first or on subsequent study. The second group of 3 fluids (Patients 17 to 19) were negative on culture and for antibodies but contained SSS. In the third group of 13 fluids (Patients 20 to 27) neither organisms nor SSS were detected but exudates from 4 of the patients contained antibodies on one or more occasions. In 3 of these, agglutinins only, and in 1, both agglutinins and precipitins were evident. A total of 6 pleural fluids from 4 patients (Nos. 16, 17, 18, 19) contained SSS, though sterile. These results indicate that the detection of SSS in "sterile" pleural effusions may reveal the pneumococcus type involved.

Table 2 records the deaths for each of the three groups, the bacteremic incidence and the relationship between the presence of SSS in the pleural exudates and in the blood. The number of cases are too few to permit statistically valid conclusions. The mortality rate of the group is 29.7% (8 deaths among the 27 patients). This table also indicates the desirability of performing various tests on body fluids, because SSS may be found in the blood when no organisms can be detected (2 patients of the first group).

Table 3 confirms this observation and shows the relationship between the determination of SSS in pleural exudate, urine, and blood.

The type distribution was found to be fairly scattered with pneumococcus Type I the most frequent (5 cases).

Of the 27 patients, 5 were treated with serum only and 1 died.

* In subsequent experiments performed by Sonia Levine in this laboratory, in two pleural fluids containing viable organisms and soluble carbohydrate the button obtained on adding serum to pleural fluid contained agglutinated organisms.

10 received sulfapyridine only and 3 died, and 12 received both serum and sulfapyridine, 4 of whom died. In the 4 cases where antibodies developed, 1 case (No. 27) died and in this case only agglutinins were found. The other 3 patients recovered, in 2 only agglutinins were present, and in the third both agglutinins and precipitins.

TABLE 2.—RELATIONSHIP BETWEEN PRESENCE OF ORGANISM AND SSS IN BLOOD AND PLEURAL EXUDATE AND OUTCOME OF DISEASE.

Culture of pleural exudate.	SSS in pleural exudate.	Cases.	Deaths.
Positive	Positive	16 7* 2†	5 3* 2†
Negative	Positive	3 2*	1 0*
Negative	Negative	8 1* 1†	2 1* 0†
Total		27 10* 2† 1†	8 (29.7%) 4* 2† 0†

* Positive blood culture without SSS.

† Positive SSS in blood without bacteremia.

‡ Positive blood culture and positive SSS in blood.

TABLE 3.—RELATIONSHIP BETWEEN DETERMINATION OF SSS IN PLEURAL EXUDATE, URINE AND BLOOD.

	SSS in pleural exudate.		Total.
	Positive.	Negative.	
Total.	7	2	9
Positive SSS in urine	3	0	3
Negative SSS in blood			
Positive SSS in urine	1	1	2
Positive SSS in blood			
Total cases	4	1	5
Positive SSS in urine			
Total cases	1	1	2
Positive SSS in blood			

Pooled serum of Groups A to F, as used for the type identification of pneumococcal SSS in urine,⁸ was successfully employed to determine the pneumococcus type involved in four experiments on pneumococcal pleural exudates. Four sterile pleural fluids obtained from tuberculous patients and used as controls did not contain detectable SSS when tested with the six different pooled sera.

The optimal concentrations of antibody (in mouse protective units) required for the detection of SSS in pleural exudates are apparently identical with those employed for the detection of SSS in urine, broth and plasma. Inhibition zones observed with other media occurred also with pleural exudates.

Two experiments were performed with SSS added to pleural exudates which contained no capsular polysaccharide. The SSS of pneumococcus Types I and III were detected in dilutions up to 1:800,000. The pH of the pleural fluids employed for these studies ranged between 7 and 7.5 (determined with "Nitrazine Paper," Squibb). These values are similar to those observed in experimentally produced pleural effusions of dogs and rabbits (Kelley, Scadron and Shinnors¹⁴).

Summary. 1. Forty-four specimens of pleural exudate from 27 patients suffering from lobar pneumonia were examined bacteriologically and immunologically.

2. Twenty-four pleural exudates from 16 patients were positive on culture, and contained detectable capsular polysaccharide, but no antibody. Capsular polysaccharide was found in 6 sterile pleural fluids from 4 patients. On one occasion the pleural culture was positive. Fourteen fluids from 9 patients were negative on culture, and contained no SSS; in 8 of these fluids (from 4 patients) antibodies could be detected.

3. Eight of the 27 patients died (29.7%). Capsular polysaccharide was detectable in the pleural exudates of 6.

4. Thoracotomy after thoracentesis was performed in 11 cases (3 deaths) while thoracenteses alone were employed for the remaining 16 patients (5 deaths). More recoveries occurred in thoracotomized patients who had had bacteremia than in those given repeated thoracenteses.

5. In 9 patients where blood, pleural exudate, and urine were studied for capsular polysaccharide it was detected in 7 pleural exudates, in 5 urines after concentration, and in the 2 bloods.

6. Pooled serum was satisfactorily used for the detection of SSS in pleural exudates.

7. For the detection of capsular polysaccharide in pleural exudates the optimal concentrations of antibody are essentially the same as those used for capsular polysaccharide detection in urine, broth and plasma.

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A METHOD OF DETERMINING THE PROBABILITY OF CONSTITUTIONAL REACTIONS DURING TREATMENT OF THE RAGWEED HAY FEVER PATIENT.*

BY WILLIAM B. SHERMAN, M.D.,

AND

SELIAN HEBALD, M.D.,

CLINICAL ASSISTANTS, DEPARTMENT OF ALLERGY, THE ROOSEVELT HOSPITAL,
NEW YORK, N. Y.

(From the Department of Allergy, The Roosevelt Hospital.)

THE occurrence of general or constitutional reactions after injections of pollen extract is one of the chief difficulties in the treatment of hay fever. Some of these reactions may be attributed to errors in technique or in judgment of dosage, but even the most experienced cannot avoid them entirely. Different patients suffering from the same type of hay fever vary so greatly in their response to treatment that the schedule of doses which is best for one may be entirely inapplicable to another.

Cooke^{1,4} has devised a method of grading the degree of sensitivity of hay fever patients in three classes on the basis of the reaction to intracutaneous tests with pollen extract of various strengths, and has planned dosage schedules for each class. This system proved helpful in avoiding reactions from the first few injections of the series, but, as was recognized by its originator and will be shown subsequently, was unreliable in predicting the further course of treatment in any particular patient.

The present paper describes the use in skin tests of an antigen derived from ragweed pollen, which gives, much better than the regular pollen extract, an index of the ability of the ragweed hay fever patient to develop tolerance for injection of increasing doses of ragweed pollen extract, and of the probability of constitutional reactions to injections.

Chemical studies have shown that there are two main distinct antigenic fractions in ragweed pollen extract which are separated by fractional precipitation with ammonium sulphate at pH 4.⁷ Practically all ragweed hay fever patients tested were sensitive to Fraction 1, some were equally sensitive to Fraction 2, while others gave little or no reaction to tests with this fraction in the dilutions ordinarily used for intracutaneous tests. When treated with regu-

* Presented before the meeting of The Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., May 3, 1941.

lar extract, which contains both fractions, almost all patients soon developed a blocking antibody^{3,5} which inactivated Fraction 1, but only 1 in 13 developed antibody which inactivated Fraction 2.⁶

It seemed that if the blocking antibody had any real importance in the body, the patients who were sensitive only to Fraction 1 and developed antibody which inactivated it should do better under treatment than those who were sensitive to both fractions but developed blocking antibody inactivating only one. When a group of 13 cases was examined from this standpoint, there was no definite difference in the clinical protection against hay fever, but there was a striking difference in their tolerance for large doses of pollen extract. The patients reacting only to Fraction 1, in the dilution tested, took doses of 1500 to 10,000 protein nitrogen units (average 5300) without constitutional reactions; those sensitive to both fractions, who developed blocking antibody only for Fraction 1, reached doses of only 700 to 2000 (average 1360), but 4 of 6 had one or more constitutional reactions. On the other hand, the one case who was sensitive to both fractions and had blocking antibody for both took doses up to 7500 without any reaction.⁶

These results suggested that the blocking antibody was a factor in the development of tolerance for antigen injections and that, indirectly, sensitivity to Fraction 2 led to a higher incidence of constitutional reactions. Therefore skin tests with the two separate fractions might give an indication of cases which were particularly apt to have untoward reactions.

Two hundred and twenty-one ragweed hay fever patients were tested intracutaneously with suitable dilutions (containing 1, 10 and 100 protein nitrogen² units per cc.) of the two ragweed fractions prepared according to the method of Stull, Sherman and Hampton.⁷ Many of these were tested because they had histories of repeated constitutional reactions, but others had taken large doses well, and still others were tested with the fractions before treatment was started, but have since received injections through one season. When the figures for all cases tested were summarized, it was found that about one-half of the patients in the whole group had one or more general reactions. Needless to say, this was considerably higher than the incidence in the clinic as a whole, due to the inclusion of so many "problem cases."

TABLE 1.—REACTIVITY OF RAGWEED-SENSITIVE PATIENTS TO FRACTIONS 1 AND 2 IN RELATION TO INCIDENCE OF CONSTITUTIONAL REACTIONS.

Intracutaneous tests.	Total cases.	Cases having constitutional reactions.	Percentage of cases having constitutional reactions.
F1 > F2	93	13	14
F1 = F2	108	81	75
F2 > F1	20	16	80

Table 1 shows the incidence of constitutional reactions in cases classified on the basis of the relative size of the skin reactions to the

two fractions. Ninety-three patients gave larger skin reactions to Fraction 1 than to Fraction 2. Of these, 13 patients (14%) had one or more constitutional reactions during treatment. Many of these were minor reactions which did not require administration of epinephrine or other drugs. However, since it is impossible to grade the severity of reactions accurately, all cases with any untoward symptoms attributable to the injections were grouped together, regardless of the severity or frequency of the reactions.

One hundred and eight patients had skin reactions of equal size to the two fractions. Of these, 81 (75%) had constitutional reactions. There were only 20 patients who showed larger skin reactions to Fraction 2 than to Fraction 1, but of these 16 (80%) had general reactions. Since the incidence of general reactions in the last two groups was more than five times that in the first group, it was apparent that these skin tests gave an index of the probability of a constitutional reaction.

However, both the theory outlined, and common sense, suggested that the actual degree of reaction to Fraction 2 was more important than the relative size of reactions to the two fractions. To compare the value of skin tests with Fraction 2 and those with regular ragweed extract as a basis for predicting constitutional reactions, we classified a group of 95 patients, A, B, and C, by the method of Cooke,¹ according as it required dilutions containing 10, 100 or 1000 protein nitrogen units per cc. of the regular ragweed extract to produce a *marked*¹ intracutaneous reaction with pseudopods. The same patients were then reclassified on a similar scale, using (for the tests) solutions of Fraction 2 containing the same amounts of protein nitrogen.

TABLE 2.—INCIDENCE OF CONSTITUTIONAL REACTIONS IN RAGWEED-SENSITIVE PATIENTS CLASSIFIED BY SKIN REACTION TO WHOLE RAGWEED EXTRACT AND TO FRACTION 2.

Class.	Total cases.	Cases having constitutional reactions.	Percentage of cases having constitutional reactions.
<i>Classified by Test With Whole Extract.</i>			
A	15	8	53
B	41	25	61
C	39	17	44
<i>Classified by Test With Fraction 2.</i>			
A	9	8	89
B	25	21	84
C	61	21	34

Table 2 shows the relative incidence of constitutional reactions in the three classes when the classification was based on tests with regular extract and when it was based on tests with Fraction 2. It was apparent that the reaction to regular extract was no criterion of the probability of general reactions. The moderately sensitive class (B) had a higher incidence of reactions than the exquisitely

sensitive class (A) and that of the least sensitive class (C) was only slightly lower. Reclassification on the basis of the reaction to Fraction 2 gave more information, Classes A and B having an incidence of reactions $2\frac{1}{2}$ times that of Class C. One weakness of this method of dividing the classes was that almost two-thirds of all the cases tested fell into Class C.

TABLE 3.—SKIN REACTION TO FRACTION 2 (100 UNITS PER CC.) IN RELATION TO INCIDENCE OF CONSTITUTIONAL REACTIONS.

Intracutaneous tests.	Total cases.	Cases having constitutional reactions.	Percentage of cases having constitutional reactions.
Slight-negative	79	10	13
Moderate	64	34	53
Marked	71	62	87

Table 3 illustrates a classification which is fundamentally the same, but in which the groups are more nearly equal in size. Here 214 cases, including some not included in Table 2, are classified on the basis of the degree of reaction to test with a solution of Fraction 2 containing 100 protein nitrogen units per cc. Seventy-nine patients gave a negative or slight reaction; of these 10 (13%) had constitutional reactions. Sixty-four patients gave a moderate reaction, without pseudopods; of these, 34 (53%) had general reactions during treatment. Of the 71 persons who gave a marked skin reaction, 62 (87%) had constitutional reactions. In other words, the group most sensitive to Fraction 2 had 7 times as high an incidence of constitutional reactions as the least sensitive, while the group with moderate reactions was midway between. While these figures tell the story fairly well, they do not reveal one important aspect. Many of the patients in the less sensitive group who were listed as having constitutional reactions had one or two reactions, often following what in retrospect seemed an unwise increase in dosage, but subsequently went on and tolerated much larger amounts. On the other hand, practically all of the patients who reached a low "ceiling" dosage, above which they could never be raised without inducing a constitutional reaction, fell into the group most sensitive to Fraction 2.

Similar information was obtained when the reaction to the two fractions was tested by the method of passive transfer. In performing these tests, sites were made on the skin of the back of a non-allergic healthy test subject by injecting intracutaneously into each site 0.1 cc. of a 1 to 10 dilution of the patient's serum. These sites were tested 48 hours later with 0.025 cc. of solutions of the respective fractions, containing 1 protein nitrogen unit per cc. In a series of 89 cases (Table 4), the group whose sera sensitized normal skin to Fraction 2 gave an incidence of constitutional reactions almost 3 times that of the group whose sera did not react with this fraction in the dilution used. However, results obtained by this method gave no information not obtainable by direct skin test.

TABLE 4.—PASSIVE TRANSFER REACTION OF SERA (1 TO 10) TO FRACTION 2 (1 UNIT PER CC.) IN RELATION TO INCIDENCE OF CONSTITUTIONAL REACTIONS.

Passive transfer reaction.	Total cases.	Cases having constitutional reactions.	Percentage of cases having constitutional reactions.
0	34	11	32
±	9	5	56
+	20	17	85
++ or +++	26	22	85

No matter how the cases were classified, there were always a moderate number of exceptions. This could have been predicted from the serologic studies which showed that some patients (about 10%) do develop a blocking antibody for Fraction 2 in the early stages of treatment, while a few others develop blocking antibody for Fraction 1 either very slowly or not at all. No attempt was made to determine the blocking antibodies in the sera of most cases. However, serum was taken after treatment from 6 patients who were definitely sensitive to Fraction 2 but had taken large doses of extract without untoward reactions. Four of the 6 sera inactivated Fraction 2, showing that their exceptional behavior was due to the type of antibody present. Because of the technical limitations of the method used,⁶ it was not possible to exclude the presence of small amounts of blocking antibody for Fraction 2 in the other two sera. On the whole, the results strongly suggested that the two fractions were specific antigens and that the blocking antibody was an important factor in acquired tolerance for injections of antigen.

More important, however, was the fact that intracutaneous tests with Fraction 2 seemed to offer a valuable criterion for judging the probability of constitutional reactions. The best basis for planning the range of doses of pollen extract for a ragweed hay fever patient is afforded by skin tests with whole extract and each fraction in dilution of 1, 10 and 100 protein nitrogen units per cc. The tests with the whole extract (and Fraction 1) give an indication, as shown by Cooke, of the safe initial dosage, while the tests with Fraction 2 indicate the probability of developing tolerance for increasing doses.

Many of the patients who gave strong reactions to Fraction 2 and were unable to take large doses of pollen extract, had excellent clinical results when treated with small doses of the regular extract. In some cases, where it was impossible to give enough of the regular extract to protect the patient from hay fever, treatment has been carried out with a solution of Fraction 1 alone. In a few cases, solutions of the two fractions have been injected separately, the dosage of each being increased according to the amount of local reaction to it. Although a few general reactions occurred, these trials suggested that many of these patients tolerate Fraction 1 better than the whole extract. However, the number of cases thus treated so far has not been large enough for final conclusions as to the degree of clinical protection.

Summary. Ragweed hay fever patients who are very sensitive to Fraction 2 of the pollen extract are less apt to develop tolerance for large doses of pollen extract than those who are only slightly sensitive to this fraction.

Intraeuteaneous tests with Fraction 2 help determine in advance which cases are more apt to have constitutional reactions and should be treated with special caution.

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STUDIES OF THE B VITAMINS IN THE HUMAN SUBJECT.

IV. MENTAL CHANGES IN EXPERIMENTAL DEFICIENCY.

By HARRIET E. O'SHEA, PH.D.,

ASSOCIATE PROFESSOR OF PSYCHOLOGY, DIVISION OF EDUCATION AND APPLIED PSYCHOLOGY, PURDUE UNIVERSITY, LAFAYETTE, IND.,

AND

K. O'SHEA ELSOM, M.D.,

ASSOCIATE IN MEDICINE, UNIVERSITY OF PENNSYLVANIA MEDICAL SCHOOL; RESEARCH FELLOW, PHILADELPHIA GENERAL HOSPITAL, PHILADELPHIA, PA.,

With the technical assistance of

RUTH V. HIGBE, M.A.,

GRADUATE STUDENT IN PSYCHOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

(From the Thompson Vitamin Clinic of the Philadelphia General Hospital, Philadelphia, Pa., and the Division of Education and Applied Psychology, Purdue University, Lafayette, Ind.)

In the course of a series of experimental studies of a deficiency of the B vitamins in man^{6-9,15} we have observed that the deficient person seems confused and apparently is less able to reason and to exhibit good judgment than under normal conditions. Experiments in the rat^{1-3,11,12,17a,b,18a-c,19-22,24-26} have shown impaired ability to learn a maze during deficiency of the B vitamins, but in no instance have accurate psychological measurements of mental changes in such a deficiency been attempted in the adult human being. Accordingly the present investigation* was undertaken to measure objectively the psychological status of the adult human subject taking an experimental diet deficient in the B vitamins and to demonstrate any changes which might occur following therapy with thiamine, brewer's yeast or the synthetic fractions of the B complex.

* We are indebted to Dr. Miles Murphy of the Psychological Clinic of the University of Pennsylvania for his cooperation.

Methods of Study. Psychological tests, grouped together as described below, were administered to 4 voluntary subjects taking an experimental diet and to 4 normal controls who consumed an adequate diet. The subjects, middle-aged women without complicating disease, were maintained under constant environmental conditions in the Thompson Vitamin Ward of the Philadelphia General Hospital. Each subject consumed a constant daily quantity of an experimental diet as described elsewhere,⁹ which supplied an adequate quantity of all dietary factors* except the B vitamins. These were present in approximately one-half the theoretically required amount† for 3 of the subjects (D. C., E. V., R. A.) and were just short of the required amount for 1 subject (I. C.). The controls, women similar to the subjects in age, general intelligence and socio-economic level, were all trusted employees of the hospital. During this study they continued their usual activities and consumed without change the same adequate hospital diet to which they had been accustomed for many years.

The study was divided into three experimental periods: Period I, when the subjects received the experimental diet alone, during which time all developed the characteristic clinical manifestations of deficiency as described elsewhere;⁷ Period II, when thiamine‡ was added to the diet and all improved, and finally, Period III, when the B complex was administered either as brewer's yeast§ or the synthetic B complex** and further clinical improvement occurred. Psychological tests were administered to the subjects at the end of each experimental period and to the controls at similar times.

PSYCHOLOGICAL PROCEDURES. Psychological tests were selected which would measure as reliably as possible those functions which appear to be impaired in human beings and rats suffering from a deficiency of the B vitamins. The mental functions studied and the psychological tests employed are shown in Table 1. Details of the testing material used are given below. With the exception of a newly devised test of prose memory and a new arrangement of the Healy-Bronner Picture Memory Test, both of which are now being standardized, all are accepted psychological tests, the limits of error of which have been carefully worked out. Alternative forms of each test, equal in difficulty, permitted repeated testing of the same mental functions without the observations being influenced by practice effects. The different forms of each test were rotated so that no one form was used for all subjects in any experimental period.

Each subject and each control were subjected to four different psychological Test Series: both Test Series A and B, given 24 hours apart, were administered at the end of Period I (Deficiency), Test Series C at the end of Period II (Thiamine) and Test Series D at the end of Period III (B complex). Each series consisted of from five to eight different psychological tests†† and, with the exception of Test Series A, each consisted of a 2-day schedule, on consecutive days as on page 390.

* Cod-liver oil concentrate capsules, used as supplement to the diet, were kindly supplied by the White Laboratories, Inc., Newark, N. J., and the ascorbic acid was supplied by E. R. Squibb & Sons, New York City.

† The theoretical requirement for thiamine was calculated for each subject according to the Cowgill formula.⁵ The thiamine content of the diet was calculated from the Cowgill tables and these values corroborated by chemical analysis on several occasions.⁹ It was assumed that other B vitamins were present in analogous quantities.

‡ The thiamine used in the studies was generously supplied as "Betabion" by Merek & Co., Rahway, N. J.

§ We are indebted to Burroughs Wellcome & Co., New York City, for supplies of "Tabloid" yeast concentrate.

** Generously supplied as "Pentaplex" by Smith, Kline & French Laboratories, Philadelphia, Pa.

†† Alternative forms of each psychological test were used in the different Test Series.

TABLE 1.—SPECIAL FUNCTIONS STUDIED AND PSYCHOLOGICAL TESTS EMPLOYED

Mental functions* studied.	Psychological test employed.
Speed of hand muscle coördination	Whipple Healy Tapping Test
Intelligence	Henmon-Nelson Test of Mental Ability, High School Examination Forms A, B and C (for a preliminary test, Otis Quick Scoring Mental Ability Test, Beta, Forms A and B)
Reasoning ability (reading)	Thorndike-McCall Reading Scale, Forms 1, 2, 3, 4, and 5
Foresight and judgment	Porteus Maze Test, up and inverted
Prose memory	Newly devised test (results to be reported later)
Visual and auditory memory	Healy-Bronner Picture Memory Test (results to be reported later)

Test Series A.

1. Whipple-Healy Tapping Test (3 repetitions).†
2. Otis Quick Scoring Mental Ability Test.‡
3. Porteus Maze Test.

*Test Series B, C and D.**First Day.*

1. Henmon-Nelson Test of Mental Ability.
2. Whipple-Healy Tapping Test.
3. Prose Memory Test.
4. Picture Memory Test—A and B.

Second Day.

1. Porteus Maze Test.
2. Prose recall.
3. Picture recall.
4. Thorndike-McCall Reading Scale.

EXPLANATION OF PSYCHOLOGICAL TESTS. 1. *Porteus Maze Test*.²³ This test presents the subject with 10 increasingly difficult mazes in which he is to trace the correct path with a pencil (Fig. 1). The mazes measure aspects of foresight and judgment since the ability to solve such a problem is determined by the subject's capacity to look ahead and to weigh different factors which lead to a decision involving action. The subject's score is in terms of the number and difficulty of the mazes with which he succeeds.

In order to have an alternative series of tests equal in difficulty, the mazes were used inverted as well as in the standard position. This arrangement was suggested by Dr. Porteus on the basis of data in his possession. A "point score" rather than the usual "age score" was employed, again at Dr. Porteus' suggestion. The mazes so used are apparently of equal difficulty, the average score for all our subjects and controls with the maze in the upright position being 68.6 and with the maze in the inverted position, 69.3 (not a significant difference). In computing results, comparison was made only between tests in which the mazes were presented in the same position.

* The statement of mental functions given here is for the purpose of clarifying the experiment for readers who are not psychologists; it is not intended to be a technical delimitation of mental "factors," "primary mental abilities" or the like.

† Some improvement in performance on this test is obtained through initial experience. For this reason it was given three times here to allow for initial improvement.

‡ Published by World Book Company, Yonkers-on-Hudson, New York City, 1937. Forms Beta A and B were used. This test was used as a preliminary exploration of the intelligence of the subjects and controls; the results were not used further in the study.

2. *Henmon-Nelson Test of Mental Ability*.^{*} This is a standardized intelligence test measuring general competency of thinking. Forms A, B and C, High School Examination, were utilized in this study. The subject's task is to follow out a variety of different directions. The original score is in points which may be translated either into terms of mental age or rate of mental growth (Intelligence Quotient).

3. *The Thorndike-McCall Reading Scale*.[†] Forms 1, 2, 3, 4 and 5. This test consists of a series of paragraphs of increasing difficulty which must be read by the subject and to each of which is attached a series of standardized questions on the content of the paragraph. The test measures the ability to read comprehendingly and may therefore be regarded as fundamentally a measure of the reasoning process.

The subject's score is in terms of the number of questions correctly answered. A translation table allows the score also to be read in terms of the elementary or high school grade reading score, in terms of reading age or in terms of a standard score called "T" score.

4. *Whipple-Healy Tapping Test*.⁴ This test presents the subject with a page of $\frac{1}{2}$ -inch squares, 10 in a row and 15 in a column. The subject's task is to place a dot with a pencil in each square across one row and back on the next, and so on, without touching any lines, making as many taps as possible in 30 seconds. Two trials are given at each testing period and the average of the two trials is the score used. The score is the number of taps made minus twice the number of errors. The speed of tapping is a highly stable phenomenon and is only temporarily subject to practice effects.¹³

5. *Test of Memorization of Short Prose Passages*. We have devised six alternative prose passages used as a test of memorization. Data from comparable age, socio-economic and intelligence groups necessary for standardization of these tests is now being accumulated and results will be reported later.

6. *Healy-Bronner Picture Memory Test*.⁴ In this test the subject views a picture while the experimenter reads to him certain relevant material. His task is to repeat as much as possible of the content of what was read while still looking at the picture. This procedure constitutes a measure of combined visual and auditory memory. Further data are required to standardize the test in this form and results will be reported later.

STATISTICAL PROCEDURES. Because the number of subjects was necessarily limited it was essential to employ extensively the statistics of small samples^{10,16} in order to arrive at a satisfactory interpretation of the results. The statistical procedures utilized will be given briefly in the present report, and a more detailed description both of the statistical handling of the data and of the procedures followed in the giving and scoring of the tests, will be published elsewhere.

CLINICAL STATUS OF THE SUBJECTS. All subjects showed definite clinical evidence of deficiency when Test Series A and B were administered; had improved, following therapy with thiamine, when Test Series C was given, and remained improved, following therapy with brewer's yeast or with the synthetic B complex, when Test Series D was given (Table 2). The degree of deficiency, as judged by the number and severity of the clinical manifestations, varied from mild to moderately severe, depending on the amount of thiamine and other B vitamins which each subject received in her diet and on the time during which the deficient diet was consumed. Thiamine was administered in varied dosage to the different subjects so that the length of time required to relieve manifestations of deficiency differed, and, therefore, the intervals between the different psychological Test Series varied

* Published by the Houghton Mifflin Company, New York City, 1935.

† Published by the Bureau of Publications, Teachers College, Columbia University, New York City, 1931.

for the different subjects. Therapeutic effect from brewer's yeast and from the synthetic B complex appeared to be comparable for the relatively short period during which these observations were made.* However, certain differences between the two have been noted when clinical observation is prolonged beyond the limits of this study.†

TABLE 2.—CLINICAL MANIFESTATIONS IN THE 4 EXPERIMENTAL SUBJECTS DURING DEFICIENCY (PERIOD I); AFTER THE ADMINISTRATION OF THIAMINE (PERIOD II); AND OF THE B COMPLEX (PERIOD III).

Subject.	Age.	Daily intake of thiamine.	Average daily excretion of thiamine during Period I, * Mg.	Clinical Manifestations.		
				Period I. (Deficiency.)	Period II. (Thiamine added.)	Period III. (Brewer's yeast or synthetic B complex added.†)
D. C.	65	205	33	(AFTER 7 DAYS)‡ Easily fatigued; anorexia; malnutrition; smooth red tongue; patellar reflex hypoactive; sense of vibration lost and muscle tenderness present in legs.	(AFTER 4 DAYS) Strength and appetite improved; incr. of 2 pounds in body weight; tongue unchanged; patellar reflex more active; vibration perceived over malleoli; muscle tenderness decr.; sl. edema.	(AFTER 31 DAYS) Strength and appetite normal; further incr. of 7 pounds in body weight; tongue less red; patellar reflexes normal; vibration perceived imperfectly in both legs; no edema.
E. V.	48	204	21	(AFTER 62 DAYS) Anorexia; epigastric discomfort; palpitation; neuritic pains in face; red tongue; sl. muscle tenderness; activity reduced.	(AFTER 10 DAYS) Anorexia diminished; epigastric discomfort unchanged; no palpitation; no neuritic pains; red tongue; muscle tenderness decr.; activity incr.	(AFTER 10 DAYS) Appetite normal; epigastric discomfort improved; incr. of 2 pounds in body weight; tongue normal; muscle tenderness decr.; activity normal.
R. A.	43	353	35	(AFTER 74 DAYS) Easily fatigued; anorexia, marked epigastric discomfort and nausea; nervousness, irritability, apprehension; red tongue; marked muscle tenderness; mod. edema.	(AFTER 8 DAYS) Strength and appetite impr.; no other change.	(AFTER 15 DAYS) Strength normal; sl. anorexia and epigastric discomfort; no nausea; no nervous manifest.; tongue normal; no edema or muscle tenderness.
I. C.	65	574	42	(AFTER 98 DAYS) Marked weakness, anorexia and epigastric discomfort; occ. vomiting; shifting abd. pain; dysp. on exertion and palpitation; abd. pain; paresthesias and pain in legs; sense of vibration impaired; marked muscle tenderness; sl. edema.	(AFTER 33 DAYS) Strength mod.; appetite fair; epigastric discomfort mod.; no abd. pain or vomiting; no cardiac symptoms; no pains or paresthesias; sense of vibration normal; mod. muscle tenderness; edema incr.; dry skin.	(AFTER 11 DAYS) Strength unchanged; appetite normal; sl. epigastric discomfort; paresthesias again marked; vibration normal; muscle tenderness incr.; edema reduced; skin impr.

* Twenty-four-hour urinary excretion of thiamine was determined daily according to a modification of the thiochrome method as described elsewhere.⁹

† Subjects D. C. and E. V. received synthetic B complex; Subjects R. A. and I. C., brewer's yeast.

‡ This subject was deficient on admission at which time Test Series A was given. She was immediately placed upon the experimental diet which was continued throughout observation.

Figures in parentheses indicate the duration of each experimental period prior to obtaining the clinical manifestations recorded, at which times the different psychological Test Series were given.

Evaluation of deficiency at end of Period I: D. C., mild; E. V., mild; R. A., moderately severe; I. C., moderately severe.

* The term "B complex" will be used in the text to denote either brewer's yeast or the synthetic B complex.

† Unpublished observations.

Results. 1. *Foresight and Judgment as Measured by the Mazes.* The subjects succeeded less well in solving the mazes (Fig. 1) when deficient than after they had received thiamine or the B complex. The mean scores for the group (Table 3) when deficient were 40 and 54.5 (Test Series A and B), as compared with 78.87 and 81.75 following administration of thiamine or of the B complex respectively (Test Series C and D). When deficient the subjects' ability to solve the mazes was inferior to that of the controls, but following therapy with either thiamine or the B complex their performance was equal to or better than that of the controls (Table 4). The difference between deficiency and recovery in each subject and the difference in the average for all subjects in deficiency and recovery

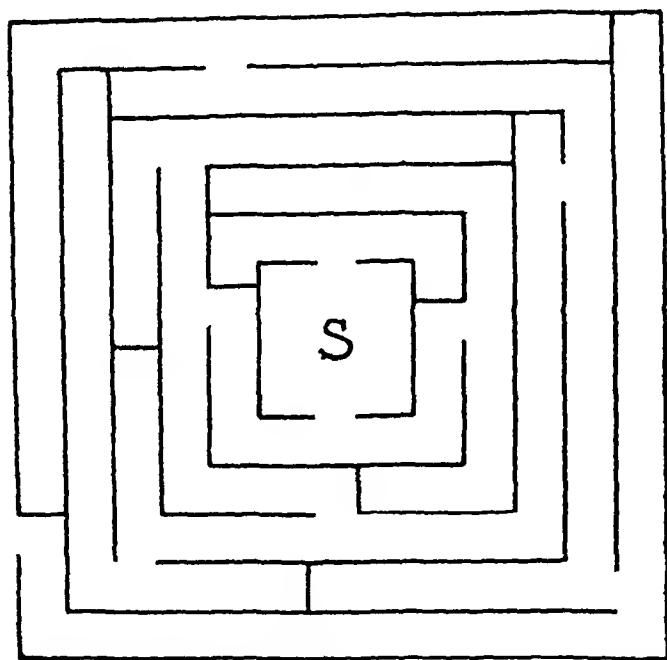


FIG 1.—A maze of moderate difficulty occupying eighth place in the series of 10. For a successful solution, the subject having placed his pencil at "S" must draw a continuous line from this point to the exit without crossing any lines, and without retracing his path at any point. (Reproduced by courtesy of Dr. S. D. Porteus, Univ. of Honolulu).

were statistically significant (Table 3). Between the subjects when deficient and the controls at the same period the difference was close to statistical significance (Table 4), suggesting that with a larger number of cases the statistical significance would be established. Furthermore, a definite relationship existed between the degree of deficiency and the degree of impairment of maze performance.* The performance of the controls, on the other hand, showed no statistically significant variation throughout observation.

* The statistical correlation between degree of deficiency and actual raw score on the mazes was determined in various ways, and the results suggest that the individual's initial score on the mazes could be fairly well foretold on the basis of his degree of deficiency.

These results indicate that deficiency of the B vitamins is associated with impaired ability to solve a series of mazes, that this impairment begins early in the deficiency and progresses as the deficiency deepens and that it may be restored by the administration of either thiamine alone or the B complex. From these facts it might be inferred that thiamine was the active factor in the results obtained and that other members of the B complex produced no further effect.* Before such an inference is acceptable observations should be made upon subjects receiving the entire complex over a prolonged period to determine whether any further improvement in maze score is possible.

TABLE 4.—AMOUNT BY WHICH THE MAZE SCORES OF THE SUBJECTS IN THE DIFFERENT EXPERIMENTAL PERIODS EXCEEDED OR FELL SHORT OF THE SCORES OF THE CONTROLS AT EACH PERIOD.

Period.	Test Series.	Differences.	Significance of differences.
		Mean of subjects minus mean of controls.	P* (.05 and less are significant).
I (deficiency)	A	-25.75	.14
	B	-18.87	.16
II (thiamine)	C	+ 8.00	.61
III (B complex)	D	- 1.62	.86
Test Series (A + B) (deficiency)		-22.31	.087†
Test Series (C + D) (therapy)		+ 3.14	.73

* See Table 3 for definition of P.

† P = .087 is calculated from the average score for Test Series A and B for each subject and control. If the difference between subjects and controls is treated on the assumption that A and B are independent tests, then P = .03.

In view of the consistent and statistically significant improvement in each subject's performance on the maze after therapy as compared with her performance when deficient and in view of the essentially constant performance of the controls over a similar period of time, it seems clear that in this group of subjects, in whom the other experimental factors were constant, the changes observed were due to the therapy employed. These observations should in no sense be construed as implying that a vitamin B complex deficiency is the only factor which may result in poor maze performance. The results may be accepted, however, as indicating that an impaired maze performance is a significant manifestation of deficiency of the B vitamins.

Morbidity alone presumably does not affect maze performance adversely. At least data obtained in studies on rats^{1,11,24} show that inanition does not reduce performance whereas a specific deprivation of the B vitamins does so. Further elucidation of this problem in the human, however, is necessary.

It appears to be well established that in order to solve a maze

* Because of the necessity of using the mazes in different positions it was not possible to compare directly the effects of thiamine and the B complex, but the improvement achieved from deficiency to the thiamine period (Test Series A to Test Series C) was analogous to that achieved from deficiency to the B complex period (Test Series B to Test Series D).

successfully one must be capable of considering a number of factors simultaneously and of choosing between the alternatives on which ultimate success depends. The exact extent to which the findings on the maze may be applied to problems of everyday life is still not certain, but one may assume that when in daily life a person deficient in the B vitamins must exercise the mental functions that are required to solve a maze, namely, foresight and judgment, he will do so less adequately than the person properly supplied with these factors.

2. *Intelligence Tests.* There was no significant difference in initial intelligence between the subjects and the controls, both being in the dull normal group of adult intelligence. Averaging the results of all the Tests, the intelligence quotient of the subjects was 85.7 (mental age 13 years and 9 months) and of the controls, 78.7 (mental age 12 years and 8 months).

No significant differences were observed in intelligence test scores during deficiency or after therapy. The controls likewise showed no significant differences from one testing period to another. These results indicate that adult intelligence test performance does not deteriorate during deficiency of the B vitamins of the degree here studied nor does it improve after therapy with these substances.

3. *Reasoning Ability (Reading).* The Thorndike McCall reading tests indicated that the subjects and controls read with a comprehension to be expected for their mental age levels. The difference between the subjects and the controls on reading score was not a significant difference. A summary of all testing periods showed the following performance:

	School Grade in reading.	Reading Age.	T* Score.
Subjects	7.3	13 yrs. 7 mos.	55.7
Controls	6.1	12 yrs. 4 mos.	48.6

* T score is a standardized score more suitable for statistical procedures than other translations of the score.

No significant changes in the subjects or in the controls were noted from any testing period to any other testing period.

4. *Tapping Performance.* Although the controls at each testing period were somewhat faster than the subjects the differences between them were within the range to be expected by chance. An average of all performances at the three testing periods for the subjects and for the controls showed the following number of taps in 30 seconds: Subjects, 74.2; Controls, 82.7.

In the case of tapping, as in that of reading comprehension and in general intelligence vitamin B deficiency apparently did not cause deterioration, nor vitamin B therapy improve tapping speed and accuracy.

Conclusions. From observations on 4 adult subjects and 4 controls we may conclude:

1. Foresight and judgment, as measured by performance on maze

tests, are impaired when the subjects are deficient in the B vitamins and are improved after therapy with thiamine or with the B complex.

2. General intelligence, reasoning ability (reading) and speed of hand muscle coördination (tapping) show no measurable deterioration when the subjects are deficient in the B vitamins and no improvement after therapy with thiamine or with the B complex.

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CHANCRE OF THE GUM. A CASE REPORT.

By JOSEPH F. SADUSK, JR., M.D.,

INSTRUCTOR IN MEDICINE, YALE UNIVERSITY SCHOOL OF MEDICINE; ASSOCIATE PHYSICIAN, NEW HAVEN HOSPITAL AND NEW HAVEN DISPENSARY,

AND

BERT G. ANDERSON, D.D.S.,

ASSOCIATE PROFESSOR OF SURGERY, YALE UNIVERSITY SCHOOL OF MEDICINE; ASSOCIATE SURGEON (DENTAL SURGERY), NEW HAVEN HOSPITAL AND NEW HAVEN DISPENSARY,
NEW HAVEN, CONN.

THE present report of a case of chancre of the gum is prompted by: 1. the rarity of this lesion; 2. the unusual appearance of chancre of the gum when compared with primary syphilitic lesions at other sites;

and 3, the fact that the syphilitic nature of the lesion may not be readily recognized.

The rarity of chancre of the gum is indicated by the estimate^{4,7} that this primary lesion accounts for only 0.46 to 1.4% of extra-genital chancres, which, though not rare, are unusual, since they constitute only 8 to 9% of all chancres. Klauder,⁴ in 1921, reporting a case of chancre of the gum, surveyed the world literature concerning this subject and found the number of cases recorded, including his own, to be 113. In 1937, Straith,⁷ reported an additional case. He carefully combed the literature which had appeared subsequent to Klauder's report and discovered 42 additional cases. The only communication noted in the literature since then has been a single case report by Scarpa⁶ which brings the total of cases reported to 157. Very few of these cases are in the American and English literature. Indeed, since Klauder's report in 1921, only 3 cases have been cited—Cabot² in 1930, Epstein³ in 1933, and Straith⁷ in 1937.

Case Report. The patient was a 19-year-old unmarried negress, a domestic, who was first seen in the Pediatric Out-patient Clinic of the New Haven Hospital at the age of 9. Following that observation, she appeared in the various Out-patient Clinics of the hospital from time to time for reasons that are irrelevant to this presentation. During this period, routine serological tests for syphilis were carried out on her blood with negative Kahn reactions being reported in 1930, 1934 and 1937.

On May 7, 1940, the patient appeared at the Medical Out-patient Clinic complaining of tenderness of the left upper gum. She reported that one week previously she had noticed a sore, red spot on the gum above the left lateral maxillary incisor. At first, it was no larger than the head of a pin, but over the period of a week it rapidly increased to almost the size of a dime. It became quite painful and bled easily when she brushed her teeth. Associated with this, a small painful lump appeared in the left side of her neck. Examination on May 7, 1940, revealed a reddish, soft, tender, raised area of gum about 1.0 cm. in diameter over the left lateral maxillary incisor and canine teeth. This lesion bled easily when touched. There was also noted an enlarged tender cervical node at the left angle of the jaw.

Following this examination she was referred to the Dental Clinic where, on May 15 and 16, 1940, dental prophylaxis was given and sodium perborate mouth washes were prescribed. Because of the unusual character of the lesion, she was returned to the Medical Clinic on May 23, 1940, complaining that the gum lesion was worse and that the lump in her neck had increased in size and had become more painful. Examination of the gum lesion on this date was as follows: The lesion was on the labial gingiva overlying the alveolar bone covering the roots of the two left maxillary incisors as well as portions of the left cuspid and right first incisor extending down over portions of the crowns of these teeth. It was about 1 cm. by 2 cm. in diameter and was uniformly elevated about 3 mm. throughout, with a clearly defined border. In contrast to the normal, firm, pink surrounding gingiva this lesion was non-pigmented, spongy, and had a bright deep red color. The dark cloudy areas scattered over the normal gingivæ which are shown in the illustration are, of course, normal pigmentation common in the colored race. The surface of the lesion glistened and was somewhat granular and cauliflower-like in appearance. There was some

bleeding but this was not excessive even on manipulation. Although the patient was quite apprehensive during the examination, the pain which she experienced when the lesion was touched or manipulated was probably quite genuine. There was regional lymph node involvement associated with the lesion, the submaxillary and anterior cervical lymph nodes being hard, moderately enlarged, and quite tender. Motion of the jaw was limited. Roentgen ray examination of the teeth under the lesion revealed no abnormalities. A Kodachrome color plate of the lesion is shown in Figure 1.

For the first time, the possibility of a chancre was considered. Serological examination of the blood on this date revealed a 4+ Kahn reaction, a 4+ Wassermann reaction with the cholesterolized antigen, and a negative Wassermann reaction with the alcoholic antigen. Repeated serological studies of the blood demonstrated a 2+ Wassermann reaction with the alcoholic antigen on May 28 and a 4+ Wassermann reaction with the alcoholic antigen on June 4. Darkfield examination of the gum lesion on May 25 was negative for *Tr. pallidum*.

Close examination of the personal history of the patient now revealed the following significant information. A 30-year-old negro, with whom the patient had been having sexual intercourse for 5 months, was examined on June 4, 1940. He was found to have mucous patches (dark field positive) in both tonsillar fossæ and on the inner surface of the lower lip. His blood revealed a 4+ Kahn reaction and a 4+ Wassermann reaction with both alcoholic and cholesterolized antigens. At the same time a 20-year-old sister of the patient, who also had engaged in sexual intercourse with the same man, was found to have mucous patches (dark field positive) in her mouth and a 4+ Kahn reaction and a 4+ Wassermann reaction with both antigens. The patient steadfastly denied acts of sexual perversion.

On June 6, 1940, following an intramuscular injection of 0.2 gm. of bismuth subsalicylate in oil, she was admitted to the Medical Service of the New Haven Hospital for antisyphilitic therapy.

Examination revealed the following significant changes: The chancre was somewhat diminished in size and in elevation and did not bleed on manipulation. It was only slightly tender to touch. In addition to the cervical adenopathy, there was a slight enlargement of the axillary and epitrochlear lymph nodes. There were no genital lesions.

The following laboratory data preparatory to therapy were secured:

Blood: R.B.C. 4,160,000, Hb. 75% (14.5 gm. = 100%), platelets, 250,000; W.B.C. 9,000, Diff. 70% seg. polymorph. neutrophils, 5% non-seg. polymorph. neutrophils; 17% lymph., 7% monos., 1% eosinophils.

Icteric Index: 6.

Urine: Clear, straw, acid reaction, sp. gr. 1.020; al. and sug. negative; centrifuged sed. negative for R.B.C., W.B.C. or casts.

Stool: Soft, formed, dark brown. Guaiac, negative. *Phenolsulphonphthalein urinary excretion:* 65% in 2 hours. *Liver function test:* No retention of bromsulphalein after 30 min.

Roentgen ray of Chest: Negative for pulmonary or cardiac lesions.

Since January, 1940, the 5-day massive dose arsenotherapy¹ of syphilis by the intravenous drip method has been employed at the New Haven Hospital² for the treatment of primary and secondary syphilis. Accordingly, this method of therapy, with the administration of a daily dose of 240 mg. of Mapharsen (arsenoxide), or a total of 1200 mg. of the drug in 5 days, was carried out on the patient from July 8 to July 12, 1940. During this period there was a slight but definite response of the chancre in that the degree of elevation over the surrounding gum was diminished, and the granular and cauliflower appearance noted heretofore changed to that of a normal smooth surface. Following this initial response the only change

noted in the lesion was the substitution of a more normal pink appearance in place of the bright red color. There still remains (March 18, 1941) a slight thickening of the gum at the site of the lesion, probably due to fibrosis and scarring.

The course of the serological changes are detailed in Table 1. It is apparent that the first serological change occurred 4 weeks after therapy and that complete seroreversal was obtained by 19 weeks' therapy.

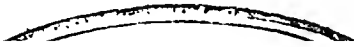
TABLE 1.—SEROLOGIC FINDINGS.

Date.	Serology.			Weeks after therapy.	Notes.
	Kahn.	Wassermann.			
		Ale. antigen.	Chol. antigen.		
1930					
Mar. 14 . . .	—				
1934					
Sept. 12 . . .	—				
1937					
Mar. 17 . . .	—				
1940					
May 23 . . .	4+	—	4+	..	Picture of gum lesion taken Darkfield examination of chancre negative
May 25	
May 28 . . .	4+	2+	4+		
June 4 . . .	4+	4+	4+		
June 8-12	Massive arsenotherapy treatment
June 19 . . .	4+	4+	4+	1	
June 25 . . .	4+	4+	4+	2	
July 5 . . .	4+	3+	4+	3	
July 11 . . .	4+	2+	4+	4	
July 19 . . .	4+	—	4+	5	
July 23 . . .	4+	—	3+	6	
July 30 . . .	4+	—	3+	7	
Aug. 16 . . .	2+	—	—	9	
Sept. 19 . . .	2+	—	—	14	
Oct. 17 . . .	2+	—	4+	18	
Oct. 25 . . .	—	—	—	19	
Oct. 29 . . .	—	—	—	20	
Nov. 5	21	Lumbar puncture; Pandy neg., 1 lymphocyte per mm. ³ , colloidal gold curve 0000000000, Wasserman negative.

Discussion. Klauder has described in detail two types of chancre seen on the gum: the abrasive or erosive type, into which group the present reported case falls, and the ulcerative type. The former is the more easily recognized type, with a smooth glistening, convex, carmine-colored surface. The border is usually sharply demarcated from the surrounding tissue and the lesion may vary in size from a few millimeters to 2 or 3 cm. in diameter. Dark-field examination for *Tr. pallidum* is usually positive. The second, or ulcerative type, is more difficult to recognize and is described by Klauder as an ulceration of variable size and configuration with or without a sharply circumscribed edge.



FIG. 1.—Chanere of the gum, May 23, 1940.



These chancres are associated with a more or less painless adenopathy of the maxillary nodes. This occurs early and the nodes are frequently of cartilaginous hardness. It is noteworthy that the chancre occurs almost always on the upper anterior gum and with surprising frequency on the left side. Location of the lesion on the posterior aspect of the gum is seen with extreme rarity.

Differential diagnosis, if the possibility of gum chancre is kept in mind, is not ordinarily difficult. Darkfield examination, serological tests for syphilis, and the presence of a marked unilateral maxillary adenopathy, usually hard and non-tender, provide the basis for the correct diagnosis in the majority of cases. Interpretation of the darkfield may, of course, be difficult at times because of the presence of spirochetes in the mouth other than *Tr. pallidum*.

The lesion must ordinarily be differentiated from hypertrophic gingivitis and epulis. Chronic or subacute hypertrophic gingivitis is usually more generally distributed over all the gingivæ. It does not tend to localize or be circumscribed, nor is it so clearly demarcated from the surrounding normal structure. Hypertrophic gingivitis commonly originates and usually extends along the marginal gingivæ and is more ulcerated. The color is less bright red and more blue as in congestion and does not show the glistening granular and cauliflower reaction seen in chancre. It is not so painful to touch nor is the patient so apprehensive, as a rule. Regional lymph gland enlargement is not a common accompaniment of hypertrophic gingivitis.

The lesion shown here may conceivably be confused with certain kinds of epulides, especially the younger vascular type. These tumors, however, have a more rounded form, are not so uniformly elevated and show a marked tendency towards pedunculation. They may have a glistening deep bright red color as seen in this case, but often tend to bleed profusely owing to the vascularity commonly observed in the early stage. Again they are not so painful to touch on manipulation nor is regional lymph gland involvement associated with them.

The authors are indebted to Mr. Howard J. Reynolds, photographer, Yale University School of Medicine, for the photography of the colored illustration in this report.

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THE DURATION OF ACTION AND THE ACTIVITY OF DIFFERENT SIZE DOSES OF PROTAMINE ZINC INSULIN.

BY HELEN EASTMAN MARTIN, M.D.,

AND

PAUL O. GREELEY, M.D.,

LOS ANGELES, CALIF.

(From the Departments of Medicine and Physiology of the University of Southern California [Los Angeles], and the Department of Medicine of the Los Angeles County Hospital.)

THE clinical literature gives no sharply defined statements on the comparative duration of action of different size doses of protamine zinc insulin. Opinions on the duration of action and time of maximum activity of a given dose vary from worker to worker. A few quotations will illustrate this diversity of opinion. Wilder¹⁰ states: "The activity of protamine insulin is prolonged for more than 48 hours in fasting diabetic patients. The duration of action of protamine insulin when food was given exceeded 36 hours." Aitken¹ says: "Observations of the effect of protamine zinc insulin on the glycosuria of diabetics receiving constant diets (usually in 3-hourly feedings) indicate that a large and possibly maximal insulin effect is exerted on carbohydrate metabolism within 3-6 hours of the injection, and that the total duration of effects of doses lying between 15 and 100 units is 15-60 hours." Neuhoﬀ and Rabinovitch,⁸ however, state that the lowest blood sugar, if protamine zinc insulin is given at 7 A.M., will be obtained in nearly all cases after 20 hours. On the other hand, if the injection is given at 10 P.M. the low point will in most cases occur after 5 hours. Others, Mark⁶ and Ricketts,⁹ in contrast speak of the constancy of action of protamine zinc insulin. Kerr and Best⁴ also conclude: "Up to a point the effect of increasing the dose of protamine zinc insulin is seen to be that of prolongation of its action rather than a further depression of the blood sugar." R. D. Lawrence⁵ is one of the few who gives any quantitative statement regarding the duration of effect of different size doses and time of maximum effect. His table of action is as follows:

Protamine zinc insulin (units)	Duration (hrs.)	Commonest time of hypoglycemia (hrs.)
10	6-8	5
20	12	8-12
30	18-24	8-20
40	24	16-24

The studies to be presented in this paper are the attempt to clarify this problem of the duration of action and the activity of different size doses of protamine zinc insulin. We were unable completely to interpret our clinical results until we had studied the

problem in the depancreatized dog. These results, therefore, will be presented first.

The depancreatized dog was selected for the study of the duration of action of protamine zinc insulin for two reasons: 1, There is no pancreas present to confuse the issue by the secretion of an unknown amount of insulin. 2, There is a fasting insulin need, or basal insulin requirement³ in these dogs. When the absorption of insulin, which has been injected, falls below the basal requirement the blood sugar rises abruptly. This gives a sharp end point for the measurable activity of injected insulin. This is a fact of real importance in determining the duration of action of protamine zinc insulin. Two depancreatized dogs were used which had a marked difference in their basal insulin requirements. This was done in order to determine the relationship of the basal insulin requirement to the duration of action of protamine zinc insulin. Dog D had a basal requirement of 0.3 unit per hour and Dog C, a low basal insulin requirement of 0.16 unit per hour.

The effects of single injections of 5, 10, 20 and 40 units of protamine zinc insulin were studied at approximately weekly intervals. The dogs were fasted for 12 hours prior to the tests and during the test. The insulin activity was measured by the amount of intravenous glucose required to maintain a normal blood-sugar level. The end of measurable activity was considered to occur when the blood sugar curve showed a rising level. (The dogs remained in good condition during the weeks of study and had no significant changes in diet or insulin requirement.) The results obtained are shown graphically in Charts 1 and 2, and are summarized in Table 1.

TABLE 1.—DURATION OF ACTION OF DIFFERENT SIZE DOSES OF PROTAMINE ZINC INSULIN IN DEPANCREATIZED DOGS.

Summary of Charts 1 and 2.

Size of dose of protamine zinc insulin (units).	Duration of measur- able activity in hours.		Peak of action in hours.		Intravenous glucose required, gm.	
	Dog D.*	Dog C.†	Dog. D.	Dog C.	Dog D.	Dog C.
5	16	20	11-16	15-19		
10	22½	24	16-22	15-24		2.7‡
20	25	51	13-20	14-24	7‡	9‡
40	25	..	12-20	..	5‡	

* Basal insulin requirement Dog D, 0.3 units regular insulin per hour.

† Basal insulin requirement Dog C, 0.16 units regular insulin per hour.

‡ More glucose could have been given as the blood sugar was in the hypoglycemic range at several points.

1. *The Duration of Action of Different Size Doses in: (a) The Same Animal.* It is obvious from the charts that the duration of action varies with the size of the dose, but is not directly proportional to the size of the dose. This is clearly illustrated by Dog D, where 5 units lasted 16 hours, 10 units 22½ hours, 20 units 25 hours and 40 units 25 hours. The actual activity of both 20 and 40 units probably lasted longer than the 25 hours of measurable activity,

but was masked by the high basal insulin requirement of this dog. In other words, the insulin being absorbed was below the amount required to maintain the blood sugar level.

Diana: Different size doses in same animal to contrast activity and duration of action

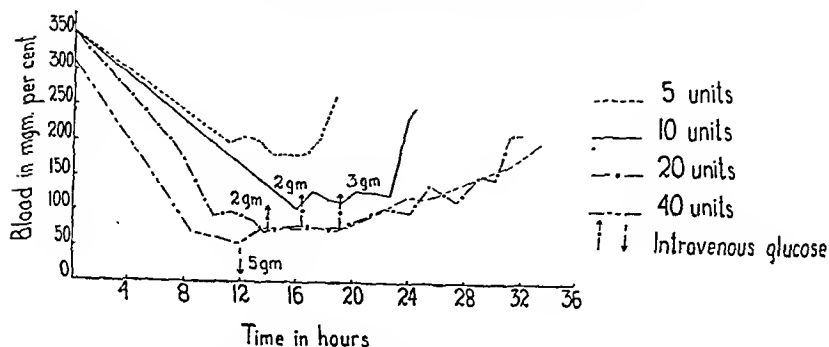


CHART 1.—Effects on the blood sugar of single injections of 5, 10, 20 and 40 units of protamine zinc insulin. The amount and time of injection of intravenous glucose is indicated by arrows. All the arrows pointing upward refer to the 20-unit curve, while the single downward arrow refers to the 40-unit curve. Basal insulin requirement 0.3 units regular insulin per hour.

Cricket: Different size doses in same animal to contrast activity and duration of action

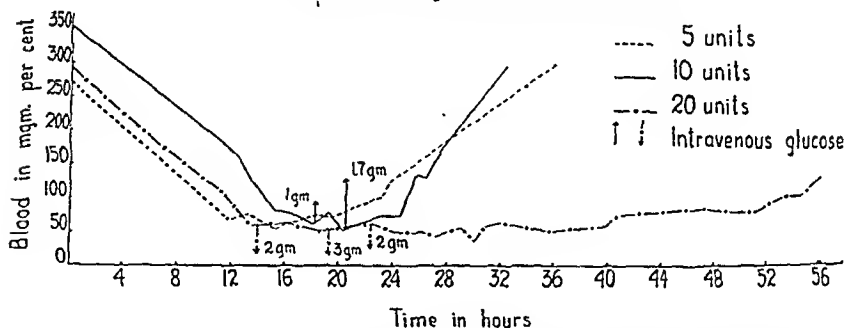


CHART 2.—Effects on the blood sugar of single injections of 5, 10 and 20 units of protamine zinc insulin. The amount and time of injection of intravenous glucose is indicated by arrows. All the arrows pointing upward refer to the 10-unit curve, while the arrows pointing downward refer to the 20-unit curve. Basal insulin requirement 0.16 unit regular insulin per hour.

(b) *Different Animals.* The difference in the duration of action of the same dose in different animals is striking. In every instance Dog C with a lower basal requirement showed a longer duration of action: 51 hours for 20 units as contrasted with 25 hours in Dog D (see Table 1).

2. *The Time Activity Function.* The gradient of fall of the blood sugar is only slightly more rapid with the larger size doses of protamine zinc insulin. This indicates that the rate of absorption is not

proportional to the size of the dose. This may be related to the fact that the surface area of the injected insulin is proportionally greater with smaller volumes. Thus in Dog D, 40 units caused a fall from 360 to 72 mg. per 100 cc. in 13½ hours and 5 units a fall from 300+ to 180 mg. per 100 cc. in 14 hours.

The time of the peak of activity appeared to vary only slightly with the size of the dose but the effect was greater with the larger size doses. This is demonstrated by comparing the activity of 5 units and 20 units in Dog D. Five units caused a moderate fall in the blood sugar level in the first 11 hours, a plateau for 5 hours and a sharply rising blood sugar level between the 18th and 17th hours. In the experiment with 20 units, 7 gm. of glucose were required between the 14th and 19th hours to prevent severe hypoglycemia. This was followed by a relatively constant blood sugar level until the 25th hour when the blood sugar slowly started to rise. The only slightly greater increase of effect of 40 units as compared with 20 units in this same dog illustrates the relative decrease in effectiveness per unit with increasing dosage, a fact well established for regular insulin.²

It should be stressed that the actual absorption of small amounts of protamine zinc insulin may last far longer than the measurable effect on the blood sugar, as explained above.

TABLE 2.—DURATION OF ACTION OF PROTAMINE ZINC INSULIN IN PATIENTS.*

Patient.	Sex.	Age.	PZI in units.	Duration of action in hrs.†	Peak of activity.	Basal rate per hr.	Glucose per os in gm.
1. F. B.	F	13	10	8	6+	1½	0
2. L. S.	M	53	30	12+	?	?	38
3. A. C.	M	26	30	24+	?	0	175
4. M. F.	F	45	30	24+	18-24 ?	?	0
5. J. S.	M	16	40	18	9-16	2+	0
6. P. Q.	M	23	40	18	?	2+	0
7. C. K.	M	73	50	23	?	?	35
8. J. D.	M	53	100	48+	24-30	½	386

* Patients received no food during test except glucose per os as required to prevent hypoglycemia.

† The end of activity was considered to occur when the blood-sugar level rose, or remained stationary for several hours.

The duration of action of a given dose of protamine zinc insulin varied from patient to patient as in the depancreatized dog. Illustrative findings are summarized in Table 2. It is apparent from these results that there is a difference in duration of action in the mild diabetic as contrasted with the severe diabetic. In mild diabetics doses of 30 units or more lasted over 24 hours and required large amounts of glucose (by mouth), to prevent hypoglycemia. This is illustrated by Patient A. C. (No. 3, Table 2) where 30 units lasted over 24 hours and required 175 gm. of glucose to prevent hypoglycemia. Severe diabetics, so classified because of a fasting

insulin requirement,⁷ showed a much shorter duration of action of comparable size doses. Thus, 40 units in Patient P. Q. (No. 6, Table 2) and J. S. (No. 5, Table 2) with high basal insulin rates, 2+ units per hour, lasted only 18 hours and required no glucose to prevent hypoglycemia.

Table 3 shows a detailed record of the results of injection of 30 units of protamine zinc insulin in a moderately severe diabetic, and Table 4 the effect of 40 units of protamine zinc insulin in a severe diabetic. Tables 3 and 4 illustrate how the results in Table 2 were obtained.

TABLE 3.—DURATION OF ACTION OF 30 UNITS PROTAMINE ZINC INSULIN IN MODERATELY SEVERE DIABETIC (M. F.), Fe 43.*

Time.	Insulin.	Blood sugar in mg. per 100 cc.
7 A.M.	30 PZI H	136
8 A.M.	155
9 A.M.	155
10 A.M.	144
12 NOON	125
3 P.M.	101
6 P.M.	136
9 P.M.	112
12 M.	86
7 A.M.	69†

* Patient fasting throughout test.

† The duration of action is over 24 hours, although the test was stopped at the 24th hour.

TABLE 4.—DURATION OF ACTION OF 40 UNITS OF PROTAMINE ZINC INSULIN IN A SEVERE DIABETIC (J. S., male, 16).*

Time.	Insulin.	Blood sugar in mg. per 100 cc.
6:50 A.M.	172.4
7:15 A.M.	40 units	
10:40 A.M.	142.8
12:55 P.M.	163.9
3:00 P.M.	153.8
8:00 P.M.	142
11:00 P.M.	133
1:16 A.M.	140
6:40 A.M.	206.2

* Patient fasting throughout test.

The end of action of the 40 units was considered to occur between the 18th and 24th hours.

The results tabulated in Table 2 also show that the peak of activity varied with the size of the dose and the basal insulin requirement, and appeared later with the larger size doses. (The peak of activity was considered to occur when there was the fastest rate of fall of the blood sugar or when the largest amount of glucose was required to prevent hypoglycemia.) To illustrate, 10 units of protamine zinc insulin in Patient F. B. (No. 1, Table 2) with a basal rate of 1½ units per hour had its peak in 6 to 8 hours, 30 units in Patient M. F. (No. 4, Table 2) with a basal insulin requirement of 1+ units per hour was probably reaching its peak at the end of 24 hours, while 100 units in Patient J. D. (No. 8, Table 2) with a

basal requirement of $\frac{1}{2}$ unit per hour, reached its peak between the 24th and 30th hours.

TABLE 5.—DURATION OF ACTION OF PROTAMINE ZINC INSULIN WITH DIET.

Patient.	Sex.	Age.	PZI units (before breakfast).	Duration of* action in hrs.	Diet, C., P., F.
1. G. B.	M	20	45	18-24	250-75-100
2. N. S.	F	14	50	24+	
3. J. D.	M	55	100†	21	250-85-60
4. C. A.	F	..	55	24+	150-65-80
5. C. McF.	F	24	100	24+	150-65-80

* Activity was taken as being at an end if the blood sugar rose from midnight to 7 A.M. (Dinner at 5 P.M.) Blood sugar determinations were made every 4 to 6 hours or oftener during the entire 24-hr. period.

† In two injections of 50 units.

TABLE 6.—PROTAMINE ZINC INSULIN WITH DIET.
(C. A. Colored Female.)

Time.	Blood sugar, mg. per 100 cc.	Diet, C. 150, P. 65, F. 80.	Urine sugar in gm.	Insulin. 55 PZI
6:30 A.M.	
7:00-7:15 A.M.	Breakfast		
9:05 A.M.	258			
10:45 A.M.	200			
8:30-10:45 A.M.	300 cc. = no sugar	
10:30-11:00 A.M.	Lunch		
1:05 P.M.	370			
3:55 P.M.	266			
10:45-3:55 P.M.	1390 cc. = 6.8 gm.	
4:30-5:00 P.M.	Dinner		
7:40 P.M.	275.8			
3:55-7:45 P.M.	500 cc. = 2.25 gm.	
11:15 P.M.	248.4			
7:45-11:30 P.M.	900 cc. = 3.06 gm.	
5:40 A.M.	138.9*			
11:30 P.M.-8:15 A.M.	1200 cc. = no sugar	

Total = 12.11 gm.

* Patient complaining of insulin reaction, given orange juice.

The results of curves of protamine zinc insulin with the diet are summarized in Table 5. Table 6 shows a sample of the type of curve from which the summaries in Table 5 were made. It is apparent from our results that it is difficult to gauge duration of effect or peak of activity with diet, since in 3 of the cases (N. S., No. 2, Table 5; C. A., No. 4, Table 5; C. McF., No. 5, Table 5) the blood-sugar level was falling at the end of the 24 hours. The post-prandial rise of the blood sugar after meals (see Table 6) masks the point activity of protamine zinc insulin during the day, so that few deductions can be drawn concerning time of maximum activity. The only period for observation is the postabsorptive period at

night. If the blood sugar falls during this period and then starts to rise abruptly one can make some deductions concerning the duration of action of protamine zinc insulin.

Discussion. When one examines critically many of the curves in the literature the reasons for the divergences of opinion are apparent: 1, Confusion exists concerning the interpretation of curves with diet, as contrasted with fasting curves. 2, No differentiation is made between the duration of measurable activity of a given dose in the severe diabetic as contrasted with the mild diabetic.

The usual curve presented to show duration and peak of activity is done with protamine zinc insulin and diet. From curves of this type few deductions can be drawn concerning peak of action or maximum activity, due to the occurrence of postprandial hyperglycemia. Only when curves are made with the blood sugar maintained in the physiologic range (80 to 150) can deductions be made concerning peak of activity. It is to be expected that the blood sugar will fall when food ceases to be absorbed at night, if there is any appreciable insulin activity present.

The majority of curves adduced to show that protamine zinc insulin has the same effect whether given in the morning or in the evening are in relatively mild diabetics or involve such large doses that activity lasts over 24 hours. As doses of 30 units last over 24 hours in mild diabetics it is obvious that cumulative effects smooth out the curve. That protamine zinc insulin does not have a constant effect in severe diabetics has been shown in Table 2. The difference between activity in the mild diabetic and the severe diabetic needs to be stressed again in this connection. It is important to give protamine zinc insulin to the severe diabetic properly timed in relation to the period when maximal insulin effect is needed. Many of the curves in the literature if examined show the points we are stressing. In the curves of Kerr and Best⁴ in the depancreatized dog although the blood-sugar levels were very low an obvious difference in duration of effect with different size doses is apparent. Thus the blood sugar started to rise after 8 hours with 1 unit per kilo of protamine zinc insulin, after 18 hours with 2 units of protamine zinc insulin per kilo and after 28 hours with 3 units of protamine zinc insulin per kilo and there was a severe reaction at 28 hours with 4 units of protamine zinc insulin per kilo.

Summary. We have shown in the depancreatized dog the following facts: 1. The duration of action of protamine zinc insulin varies with the size of the dose, but is not proportional to the size of the dose.

2. The duration of measurable effect varies with the basal insulin requirement of the animal. A dog with a high hourly basal insulin requirement has a shorter duration of action of a given dose than a dog with a low hourly basal requirement.

3. The peak of activity varies slightly with the size of the dose, but the total activity is greater with the larger size doses.

Applying these facts to diabetic patients, the following conclusions were reached: 1. There is a difference in duration of action of a given dose of protamine zinc insulin in the mild diabetic, with no basal insulin requirement, and in the severe diabetic with a basal requirement. The duration of action of protamine zinc insulin in the severe diabetic is influenced by the basal insulin requirement of that individual.

2. There is a period of maximum activity with all size doses of protamine zinc insulin and this period is delayed with the larger size doses.

3. Curves of activity with diet are difficult to evaluate unless rigid criteria are used. A falling blood sugar in the postabsorptive period at night gives little information either as to intensity of activity or duration of activity of a given dose. A falling blood-sugar level followed by a rising level will give information as to the duration of action.

4. The importance of these results in proper timing of insulin dosage in the severe diabetic is discussed.

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OBSERVATIONS ON THE ORAL ADMINISTRATION OF CITRATED BLOOD IN MAN.

II. THE EFFECT ON THE STOOLS.*

By LEON SCHIFF, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, UNIVERSITY OF CINCINNATI MEDICAL SCHOOL,

RICHARD J. STEVENS, M.D.†

FORMERLY ASSISTANT IN MEDICINE, UNIVERSITY OF CINCINNATI MEDICAL SCHOOL,
AND

NATHAN SHAPIRO, M.D., AND SANDER GOODMAN, M.D.,†

INSTRUCTORS IN MEDICINE, UNIVERSITY OF CINCINNATI MEDICAL SCHOOL,
CINCINNATI, OHIO.

(From the Department of Internal Medicine, University of Cincinnati Medical School, and the Gastric Laboratory of the Cincinnati General Hospital.)

In the management of patients with hematemesis or melena it is important to determine the severity of the hemorrhage and whether

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† Justin A. Rollman Fellows in Internal Medicine, 1938-1939, and 1937-1938, respectively.

or not the bleeding has stopped. In this connection one frequently finds the clinician assuming that the patient has had a severe hemorrhage because he has passed a tarry stool, and that the patient is still bleeding because he continues to pass tarry stools or because his stools continue to give a positive chemical test for occult blood. In order to test the validity of these assumptions it was decided to give patients and normal controls known amounts of citrated human blood either orally or by stomach tube and to observe the effect on the stools.

The Amount of Blood Necessary to Produce a Tarry Stool. The subjects used in this study consisted of 3 normals and 15 ward patients varying in age from 23 to 72 who, with one exception, were free of digestive tract disease. Citrated venous blood, 2 to 3 weeks' old, was mixed with 100 to 200 cc. of charged artificial Vichy water* to help disguise the taste and was then administered orally. Before the blood was given to any subject, at least two of his stools were found to be of normal color. A regular diet was allowed, and drugs known to discolor the stools were prohibited. When blood was given more than once, an interval of 10 days was allowed to elapse before the succeeding dose was administered. When a tarry stool was once obtained, no more blood was given.

TABLE 1.—THE AMOUNT OF CITRATED BLOOD REQUIRED TO PRODUCE A TARRY STOOL.

Amount of blood administered (cc.).	No. of subjects receiving blood.	No. with tarry stools.	No. without tarry stools.
50	7	0	7
75	9	0	9
100	7	4	3
125	3	1	2
150	4	1	3
175	2	1	1
200	2	2	0

It will be seen from Table 1 that tarry stools were obtained in individuals given from 100 to 200 cc. of blood. The 4 individuals who passed a tarry stool after 100 cc. of blood did not pass such stools when given 50 or 75 cc. of blood, while the other 5 who passed tarry stools did not do so when given at least one smaller dose than the one which produced a tarry stool. These values are higher than those of 50 to 80 cc. reported by Daniel and Egan¹ in a study comprising a group of 10 healthy medical students. The difference in results may be explained either by the fresh blood used by these authors or by a less rigid criterion of a tarry stool. The designation

* Kindly furnished by the W. T. Wagner's Sons Company.

"tarry" was applied by us only to a glistening stool having the same black color as found on a standard paint color chart.*

Appearance and Duration of Bloody or Tarry Stools After Intra-gastric Administration of Citrated Blood. The blood used in this phase of the study had been stored in the blood bank at the Cincinnati General Hospital for 3 weeks and was kept at room temperature for an hour before it was administered. The blood was given by stomach tube in quantities of 1000 to 2000 cc. With amounts of 1000 cc. it was allowed to flow by gravity into the fasting stomach through a Rehfuß tube during a period of 30 to 60 minutes. When a total of 2000 cc. was given, the blood was divided into amounts of 700, 700, and 600 cc. and was introduced at 4-hour intervals. A hypodermic injection consisting of codeine sulphate, gr. 1, and atropine sulphate, gr. $\frac{1}{50}$, preceded the administration of the blood in order to prevent too rapid passage through the intestinal tract.

TABLE 2.—APPEARANCE AND DURATION OF BLOODY OR TARRY STOOLS AFTER INTRAGASTRIC ADMINISTRATION OF CITRATED BLOOD.

Subject.	Amount of blood given (cc.).	Appearance of 1st bloody stool (hrs.).	Appearance of 1st tarry stool (hrs.).	Duration of bloody or tarry stools (days).	No. of bloody or tarry stools.
W. S.	1000	12	..	1	5
S. W.	1000	17	..	1	3
F. O.	1000	4	..	3	4
J. G.	1000	9	20	3	5
C. E.	1400	4	24	5	8
F. F.	2000	..	20	4	3

Table 2 shows that following the administration of such quantities, the blood may appear in the stools within 4 hours and that the patient's stools may be entirely bloody and never tarry, presumably as a result of intestinal hypermotility. Three of the 4 subjects receiving 1000 cc. of blood had no tarry stools whatever, the stools possessing a reddish cast following which they became a dark brown. Thus a grossly bloody stool does not necessarily indicate that the blood is entering the intestinal tract low in the small intestine or in the colon.

The number of bloody or tarry stools is not directly related to the amount of blood ingested, since, for example, W. S. had 5 bloody stools after 1000 cc. of blood, whereas F. F. had but 3 tarry stools after 2000 cc. of blood, while C. E. had 8 bloody or tarry stools after 1400 cc. of blood. Bloody stools may be passed for as long as 3 days and tarry stools for as long as 5 days after the administration of a single quantity of blood.

It was of interest that none of the subjects vomited the blood.

* In a previous report,⁵ we stated that "we have occasionally obtained tarry stools following the oral administration of 75 cc. of blood, but in order uniformly to obtain tarry stools, we have had to give 100 to 150 cc. of blood." At this time our criterion of a tarry stool was not as rigid as the one referred to in this paper, and the number of observations was less.

Duration of a Positive Test for Occult Blood in the Stools After Oral or Intragastric Administration of Citrated Blood. Hesser² made the interesting clinical observation that following hematemesis or melena in patients with bleeding peptic ulcer, occult blood is usually present in the stools for a period of 2 to 3 weeks. (It might disappear within 1 week or persist for as long as 5 to 6 weeks after hemorrhage.) Our observations listed in Table 3 are largely in keeping with this author's observations, since following the administration of a large dose of blood, the stools may show a positive test for occult blood for as long as 14 days. The fact that Hesser obtained positive tests for longer periods may be explained by his larger number of observations (72 patients), by the fact that in some of his patients bleeding may have continued or recurred after admission to the hospital, and by slowing of the intestinal motility in his cases as a result of bed rest and restricted diet.

TABLE 3.—DURATION OF A POSITIVE TEST FOR OCCULT BLOOD IN THE STOOLS AFTER ORAL OR INTRAGASTRIC ADMINISTRATION OF CITRATED BLOOD.

Subject.	Amount of blood given (cc.).	Method of administration.	No. of stools giving positive test		Duration of positive test (days)	
			with		with	
			Benzidine.	Guaiac.	Benzidine.	Guaiac.
J. T. . . .	125	Oral	3	3	3	3
	175	Oral	4	3	5	2
	250	Oral	7	7	10	10
G. R. . . .	75	Oral	4	2	4	2
	125	Oral	3	2	5	3
S. W. . . .	1000	Intragastric	7	9	4	5
F. O. . . .	1000	Intragastric	11	10	8	8
C. E. . . .	1400	Intragastric	13	10	11	11
F. F. . . .	2000	Intragastric	12	10	14	12

The subjects used in this phase of the study were on a meat-free, green vegetable-free diet at the time they were given the blood and had shown preliminary negative tests for occult blood in the stools.

Summary. A tarry stool may result from the ingestion of 100 cc. or more of citrated human blood. Following the intragastric administration of 1000 to 2000 cc. of citrated human blood, gross blood may appear in the stools and tarry stools may continue for 5 days and may number as many as 8. Positive chemical tests for occult blood in the stools may persist for as long as 10 days after ingestion of 250 cc. of citrated human blood or for 12 days after intragastric administration of 2000 cc.

Conclusions. The passage of a tarry stool does not necessarily indicate the occurrence of a severe hemorrhage into the digestive tract. The persistence of tarry stools or occult blood in the stools does not necessarily indicate the continuation of such hemorrhage.

We wish to express our thanks to Dr. Paul Hoxworth, Director of the Red Cross Transfusion Service, for his coöperation in this study.

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CALCIUM BILE.

A CLINICAL AND PATHOLOGICAL STUDY.

BY MARSH MCCALL, M.D.,

CLINICAL INSTRUCTOR IN MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY,

AND

ALLAN TUGGLE, M.D.,

RADIOLOGIST, CHARLOTTE MEMORIAL HOSPITAL,
CHARLOTTE, N. C.

(From the Departments of Medicine and Radiology, The New York Hospital and Cornell University Medical College, and the Charlotte Memorial Hospital.)

LESS than a half dozen clinical reports have appeared in the American and foreign literature in regard to calcium bile. The earliest report of white bile was made by Churchman¹ in 1911, who reported that an analysis of the gall bladder contents revealed calcium salts. Volkmann¹¹ in 1926 was the first observer to use the term "milk of calcium." In 1931, Phemister⁹ and his coworkers made an analysis of 7 patients with calcium carbonate gall stones, 5 of whom were subjected to operation. This was followed in 1933 by Knutsson's³ group of 12 patients showing calcium carbonate deposits in the gall bladder. Kornblum and Hall⁴ in 1935 outlined the roentgenologic findings in a series of 5 patients seen at the Hospital of the University of Pennsylvania.

We have been able to survey the gall bladder material seen in the New York Hospital during the past 8 years which, subsequently, proved to be calcium bile at operation and was confirmed by study of the surgical specimen. During this period we have found 15 patients who fulfilled our criteria, and the specimens from whom were examined in the pathologic laboratory.*

It has been interesting to scrutinize these patients from the standpoint of sex distribution, duration of symptoms, icteric index, biliary study, roentgenologic findings, pathologic summation and follow-up study after 1 year. Table 1 gives a brief summary of these data.

It is readily observed that the age and sex distribution is not unlike that found in the usual gall bladder study. All of our patients complained either of right upper quadrant or epigastric distress with excessive gas. There was not a single instance of jaundice noted in the clinical histories, nor was there any evidence of clinical jaundice as shown by the icteric index studies. Biliary drainage was performed in 10 of the patients, and in none of these trials was a B-fraction obtained. A history of typhoid fever was not elicited in a single instance. Bile cultures taken after operation were negative in 8 patients, and not carried out in the others.

* We are indebted to Dr. N. Chandler Foot for the use of his histologic material.

Only 1 of our patients was acutely ill at the time of hospitalization. At operation the cystic duct was found occluded, constricted, or surrounded by indurated tissue in every patient. The mucosa was absent in 4 specimens (Fig. 1) and evidence of chronic cholecystitis was seen in all microscopic sections (Figs. 1 and 2). In this series of patients, we could not demonstrate hypertrophy of the muscularis as described by Knutsson.³ The calcium carbonate paste was occasionally stained with bile pigment. In 1 instance, the paste was described as black and in 5 others the material was chalky white. Chemical examination carried out in 1 instance showed 76.9% calcium carbonate.*

TABLE 1.—RÉSUMÉ OF THE CLINICAL AND PATHOLOGIC STUDY.

Case No.	Age.	Sex.	Duration (yrs.).	Icteric index.	B. bile.	Lesions found.	Follow-up (1 yr.).
1	54	F	3	8	None	Stone in cystic duct	Well
2	48	F	4	6	None	Chr. cholecystitis	Well
3	50	M	4	10	Unknown	Cystic duct small	Well
4	51	M	3	12	Unknown	Chr. cholecystitis	Well
5	33	M	2	5	None	Stone in cystic duct	Well
6	50	F	8	6.8	None	Mucosa absent	Well
7	58	F	3	7	None	Cystic duct constricted	Well
8	20	F	1	Unknown	None	Mucosa absent	Well
9	41	F	2	6	Unknown	Cystic duct small	Well
10	45	F	3	7.5	None	Chr. cholecystitis	Well
11	49	F	3	Unknown	None	Stone in cystic duct	Duodenal ulcer
12	46	F	1	6	Unknown	Cystic duct small	Well
13	35	F	1	5	Unknown	Strawberry gall bladder	Well
14	31	F	5	5	None	Cystic duct surrounded by indurated tissue	Well
15	44	F	2	6	None	Chr. cholecystitis	Well

It goes without saying that a single chemical examination of 1 specimen fails to prove that all the specimens contained calcium carbonate. As we proposed this investigation to be a clinical one, we did not deem it essential to carry out further chemical analyses. Furthermore, every patient was independently diagnosed by the roentgenologist and, subsequently, by the pathologist.

* The specimen weighed 2.2915 gm. and 3 days later 2.2755 showing a loss of 16 mg. on standing due to evaporation (drying). The specimen was mixed about 250 cc. of water and allowed to stand 67 hours, in the hope that all the calcium carbonate would settle and that the nearly clear fluid might be decanted and filtered. The deposit weighed on drying, 1.7 gm. An aliquot part of the liquid was treated with HCl, evaporated and then incinerated. The result indicated that 250 cc. yielded (or would have yielded) 200 mg. of calcium chloride, corresponding to 190 mg. of calcium carbonate (CaCO₃). A part of the dried residue weighing 500 mg. was converted into the chloride and incinerated. The ash weighed 503 mg., corresponding to 459 mg. of calcium carbonate; hence the 1.7 gm. contained 1.56 gm. of calcium carbonate. This added to the 190 mg. obtained from the decanted liquid equals 1.75 gm. or 76.9% of the original weight of the specimen—2.2755 gm.

A preoperative diagnosis of milk of calcium bile is strictly radiographic. If and when a scout film (Fig. 4) is made, the diagnosis is relatively simple. Here we find a calcification in the upper right quadrant which is to be differentiated from other calcifications occasionally found on the flat film such as calcified nodes, cysts, stones,

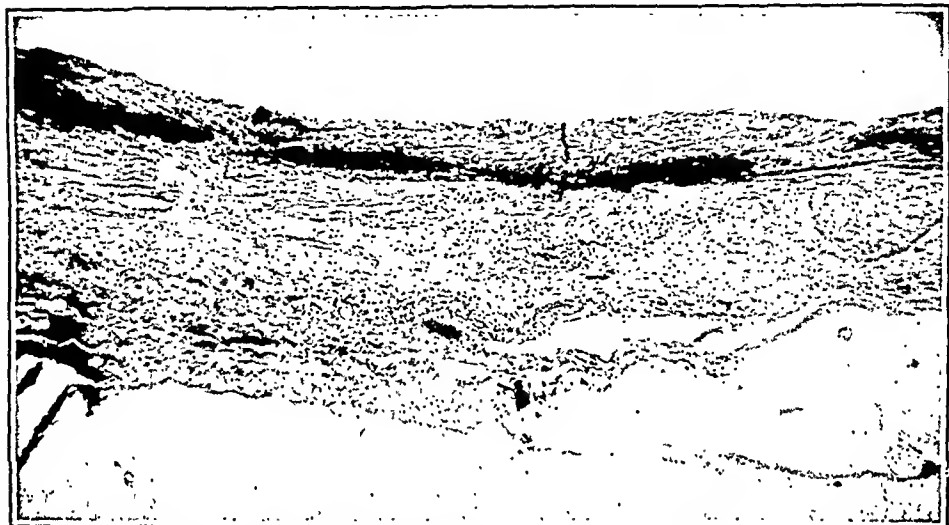


FIG. 1.—(No. 138959.) Gall bladder with no cellular exudate in submucosa. Only a few strands of muscle tissue remain.



FIG. 2.—(No. 244379.) Gall bladder shows an increase in fibrous tissue throughout with many lymphocytes and leukocytes. There was no muscular hypertrophy.



FIG. 3.—Pathologic specimen. Before operation the films showed a smooth shadow which did not change in size following the high fat meal.



FIG. 4.—(No. 138959.) Shadow is due entirely to limy bile taken before the dye was ingested.

calcified gall bladder, or unilateral costal cartilage calcification. The limy bile shadow is quite homogeneous except when negative stones are present. The density varies, depending upon the calcium content, and the shadow may be barely perceptible or quite dense. If the calcium material is thin, the opaque shadow may change in shape from day to day, but it will always be present. In case a preliminary scout film is not made, there is often difficulty in deciding whether the shadow seen is that of the dye-filled gall bladder

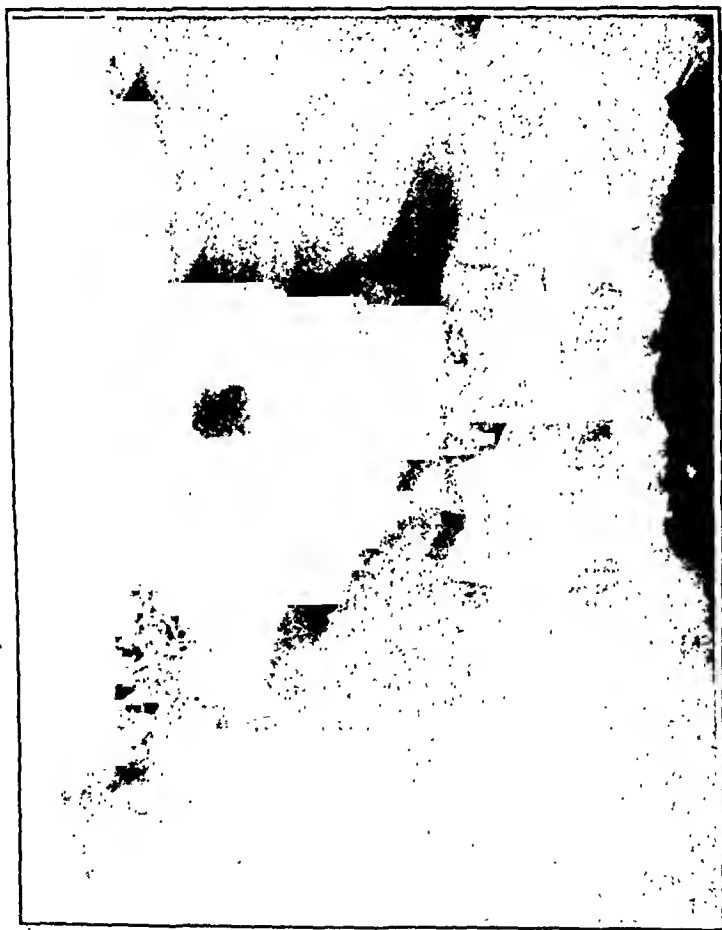


FIG. 5.—Shadows of calcium density in the region of the cystic duct and in the fundus.

or of calcium carbonate bile. The first suggestion that calcium bile may be present is noted when the gall bladder does not decrease in size following ingestion of a high fat meal. This in itself is not pathognomonic. Many gall bladders are seen which have not changed their size on the postfatty meal film, but in this case a subsequent flat film of the gall bladder should be taken. This is particularly true when either definite or questionable stone shadows are seen in the region of the cystic duct (Fig. 5).

The presence of calcium bile should be suspected when a visible gall bladder of calcium density is seen without cholecystography. This impression may be further fortified if the gall bladder is visible and an opaque stone is noted in the cystic duct. A gall bladder containing milk of calcium bile often shows no change before or after the fat meal. Atypical shadows unlike gall stones which are found in association with a non-visualized gall bladder during cholecystography should be regarded with suspicion. The diagnosis of calcium bile is entertained when: 1, a visualized gall bladder is seen in roentgenograms without cholecystography or observed roentgenoscopically during a gastro-intestinal study; 2, no change in the appearance of the gall bladder is seen in the cholecystogram after a fatty meal; 3, there is a change in the shape of the visualized organ; 4, gall bladder shadow persists after cholecystography; 5, a stone in the cystic duct is seen with a visualized gall bladder; 6, when shadows unlike gall stones are found in association with a non-visualized gall bladder during cholecystography.

Discussion. The formation of calcium bile and carbonate gall stones are probably closely related. Wilkie¹² was able to reproduce calcium calculi in rabbits. He found that upon ligation of the cystic duct in the presence of cholecystitis that calcium stones were formed. He concluded that the cystic duct must be occluded by some process before certain changes occur in the physiology of the gall bladder leading to subsequent mucosal effects in the duct and the wall of the organ. In due time, he concluded, there would be an increase in the excretion of calcium from the gall bladder. We believe that a chronic inflammatory process with partial-obstruction of the cystic duct is essential to calcium carbonate formation. Whether the calcium is derived from the gall bladder wall is an unsettled question, although Phemister⁹ and his coworkers were able to demonstrate the presence of calcium only in the gall bladder side of stones found in the cystic duct. Schubb and Goodstone¹⁰ believe that calcium in the gall bladder is increased in the presence of inflammation alone.

Lichtwitz⁵ suggested that the character of the bile reaction influenced the formation of the deposits found in human bile. Naunyn⁶ advanced the view that a *special* biliary reaction may be necessary for carbonate deposition. Okada⁸ noted the difference in reaction between gall bladder bile and liver bile in the dog, as did Neilson and Meyer⁷ for the rabbit, and these observations were largely confirmed by Drury, McMaster, and Rous.² The latter state that normal liver bile is alkaline with an average pH of 8.2; but in the gall bladder, the secretion undergoes a change toward the acid side with a pH of 5.18 to 6. It would appear, therefore, that when a gall bladder has been damaged by any cause, it may be unable to alter the character or the pH of the bile coming from the liver. This change may play a rôle in the precipitation of calcium salts.

Therefore, no definite conclusion can be drawn as regards the etiology of calcium bile. Its secretion from the wall of the gall bladder, as assumed by Phemister,⁹ has not been proved by any experiment so far as we know. When the cystic duct is partially occluded by stone, or by inflammatory induration, it is possible that the organ may develop abnormal physiologic functions. It is more likely, however, that the precipitation of calcium bile occurs subsequent to the reduction in the cholesterol and bile-salt content of the bile which, in turn, is secondary to the inflammatory changes seen in all of our specimens. It was Knutsson's³ belief that the wall of the gall bladder was hypertrophied, due to obstruction in the duct, but we were unable to demonstrate such a change in our specimens. On the other hand, we do agree with his assumption that the calcium salt is precipitated from the bile itself when the outflow from the gall bladder is hampered by obstruction of the cystic duct. This phenomenon occurs only when certain mucous membrane changes have interfered with the absorptive and excretory functions of the organ.

Summary. We have reported 15 patients with calcium bile demonstrated by scout films and corroborated by examination of the surgical specimens. The clinical facts have been outlined and the salient features noted in the histologic study have been discussed. Finally, various theories to explain this disturbance of calcium metabolism in the bile have been presented.

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THE DIAGNOSIS, INCIDENCE, AND SIGNIFICANCE OF ESSENTIAL ACHLORHYDRIA.

BY ASHER WINKELSTEIN, M.D.,

ASSOCIATE IN MEDICINE AND PHYSICIAN IN CHARGE OF THE GASTRO-INTESTINAL CLINIC,
THE MOUNT SINAI HOSPITAL; ASSOCIATE IN MEDICINE, POST-GRADUATE SCHOOL
OF MEDICINE, COLUMBIA UNIVERSITY, NEW YORK, N. Y.

(From the Gastro-Intestinal Clinic of The Medical Department, The Mount Sinai Hospital.)

In recent years, there has arisen a renewed interest in the subject of achlorhydria. This is chiefly due to the demonstration by Castle and his coworkers of an "X" substance in gastric secretion

closely related to pernicious anemia. However, achlorhydria is not only of importance in pernicious anemia, but is also prominently involved in the following conditions: gastric carcinoma, chronic gastritis, gall bladder disease, Graves' disease, tuberculosis, gastrogenous diarrhea and other gastrogenous intestinal disturbances; chronic arthritis, alcoholism, subacute combined sclerosis, anorexia nervosa, sprue, pellagra, gastric lues, Simmonds' disease and achlorhydric anemias. A complete discussion of the significance of these achlorhydrias would take us too far afield. Bloomfield and Pollard² have discussed the entire subject in a monograph to which the reader is referred.

The terms "anacidity," "achlorhydria" and "achylia gastrica" have been used loosely in the past. "Anacidity" should be dropped since practically every sample of gastric contents is on the acid side of pH 7. "Achyilia gastrica," a term introduced by Max Einhorn, signifies an absence of gastric secretion. Since gastric secretion may contain free hydrochloric acid, pepsin, rennin, lipase, mucin, some diluting secretion, and the intrinsic "X" substance of Castle, it is doubtful if true achylia gastrica ever occurs. The term might properly be retained for absence of free acid and ferments, provided such a definition is given specifically by each author.

The word "achlorhydria" means the absence of free hydrochloric acid. The subject of achlorhydria is, even at the present time, in a very confused state. Precisely what is meant by achlorhydria is neither clear in the theoretical discussions nor in practical clinical medicine. Certain questions arise. How is the achlorhydria diagnosed: by what type of test meal, by what indicators? Do we mean by achlorhydria a failure to react to Toepfer's solution, or to color Congo red paper blue? Do we mean a certain pH (3.5) or over? Are we interested in the achlorhydria that may occur in an individual's stomach during the normal course of digestive events in his life (that is, during, after, and between his usual meals)? Are we concerned with transient, temporary achlorhydria, or, are we considering only permanent achlorhydria? In other words, is it the false or transient ones and even the relative subacidities that interest us, or, is it the absolute, true, complete, and permanent achlorhydrias? From these questions alone, the complexity of the problem is patent. Probably it will be necessary to restudy the old investigations and institute new ones in order to answer these questions. Perhaps all of them are of importance and require emphasis and analysis.

From the heterogeneous group of these achlorhydrias we have selected one type for study, namely, the true or absolute achlorhydrias. By a "true achlorhydria" we mean a pH of 3.5 or over, one that is complete, and more or less permanent; in other words, a state in which the stomach is incapable of secreting free hydrochloric acid even under maximal stimulation.

At this point we will review briefly the work of other recent

investigators. We agree with these authors in their main contention that true achlorhydria should and does occupy an important place in present-day clinical medicine. We differ from them in the normal incidence of this condition when it is unassociated with ascertainable organic disease. Their high figures, we believe, are largely due to the inadequate methods used in investigating patients' with apparent achlorhydria.

Certain writers (Zagal, Marks and Kantor⁹) using the Ewald test meal, without a fractional meal or a histamine test as a control, give the incidence of achlorhydria as follows: In 7679 cases studied, 564 (7.3%) had achlorhydria. The incidence increased from 2% to 5% in the first three decades of life to 16% to 22% in the sixth, seventh, and eighth decades. Using a modified Ewald test meal continued for 2 hours, a careful study of the achlorhydria cases was reported from the Mayo Clinic. In a study of 3746 records, Vanzant and collaborators⁶ reported the incidence of 12% and the figures ranged from a 4% occurrence at the age of 20, up to 23% to 26% in the aged. This very high incidence may be due to a difference in the material or more probably to the method of study—usually the Ewald test meal. As was stated in their article, "unfortunately the control study with histamine was made in only a small per cent of the cases." In the study of achlorhydrias reported by Boekus, Bank and Willard³ their incidence was 5.7% in a series of consecutive gastro-intestinal cases. However, if one removes from this group the cases which secreted free acid after histamine and also the cases with a recognized etiology, the incidence of true achlorhydria of unknown etiology drops in their series to 2.2%.

We are presenting our experience with this particular phase of the subject for the following reasons: 1, our cases have been studied repeatedly; 2, the method of study differs from those previously used; 3, our results differ strikingly from those usually given in the literature; 4, using these methods of study, it is possible to isolate and describe with greater accuracy the separate group of "true achlorhydrias."

We will next discuss the methods of studying the stomach for the presence or absence of the acid secretion. The diagnosis of achlorhydria has successfully passed through the stages of the Ewald test meal, of repeated Ewald test meals, the Riegel test, the various types of the fractional test meal, the histamine test, the combined tests (urinary and gastric acidity studies) and the chromoscopic procedure (neutral red). The ideal method of establishing the fact as to whether the stomach is capable of secreting free hydrochloric acid under the usual daily conditions of living would be to leave an indwelling catheter in the stomach 24 hours daily and, using either constant suction or repeated aspirations, or, preferably, an indwelling H-ion electrode, test the gastric contents for free acid throughout the 24 hours of the day. We have already studied the

gastric secretion throughout the 24 hours in some patients with duodenal ulcer while on the Sippy treatment to ascertain the degree of neutralization throughout the day and night. Also, in a large series of cases, we approximated this ideal by doing a 3-hour oatmeal gruel fractional test meal during the day, plus a fractional study of the gastric secretion throughout the night. These studies (reported elsewhere⁷) are, of course, impractical for the investigation of ambulatory private and outpatient department patients. Also, they do not answer the question in which we are chiefly interested, as to whether the stomach is incapable of secreting free hydrochloric acid at any time under all conditions and especially under the influence of the greatest stimulation to secretion. After working with several methods, chiefly the oatmeal gruel and alcohol fractional test meals, the histamine test and the neutral red test, we arrived at a combined method which we believe is a satisfactory test for the ability of the stomach to secrete free hydrochloric acid.

In evolving this test we have considered the present state of our knowledge of the physiologic mechanisms involved in gastric secretion (Babkin¹). The normal human stomach is first stimulated to secrete over nervous pathways. The thought, sight, taste, smell and odor of food acts as a stimulus to the fundus glands through the vagus nerve and accounts for a considerable amount of the gastric secretion. Following this initial stage (or even without it) certain secretagogues and food substances (split and unsplit) act in and through the antrum to produce some substance (probably a hormone) which after absorption act without nervous intervention through the blood stream on the fundus glands and account for the prolonged gastric secretion which is necessary to complete gastric digestion. While the upper small intestine is chiefly the site of inhibitory stimuli, a certain amount of gastric secretion is produced (also chemically) through intestinal stimuli. As a result of these considerations it is necessary to have a test which will stimulate the psychic and chemical phases maximally. For various reasons oatmeal gruel was chosen as the test meal. It is considered an efficient stimulus to the nervous phase of gastric secretion and in itself neither neutralizes nor absorbs free acid nor does it stimulate mucin excessively. Also, it has been used so widely by numerous workers that it affords a better basis of comparison than other test meals.

Histamine was employed simultaneously. This is a powerful direct chemical stimulant of the acid-secreting parietal cells. Since we had confirmed the original work of Glaessner with neutral red, we included this test. In a previous study⁸ we had found that when neutral red is injected intramuscularly it will not appear in the gastric contents within 2 hours if the stomach cannot secrete free acid. This dye is a specific indicator of the ability of the parietal cell to secrete acid. Thus, by combining the three tests,

food, histamine, and neutral red, we subject the acid cells to a good food stimulus, to a powerful chemical incitant, and to what seems to be an excellent indicator of cell function. While still not entirely ideal from the theoretical point of view, this type of combined test for gastric secretory function seems to be the most complete and intensive method of study used to date. The details of the combined test will now be described.

Method. The patient presents himself in the morning in a fasting state. The thin Rehfuß or Levin tube is passed and the fasting contents aspirated. Histamine (Imido-Roche) (0.5 mg.) is injected subcutaneously and, at the same time, 40 mg. of neutral red dissolved in 1 to 2 cc. of sterile distilled water is injected intramuscularly. The patient then drinks 150 cc. of strained oatmeal gruel. A sample is aspirated every 15 minutes for 2 hours in the outpatient department and for 3 hours in the wards of the hospital. The samples are tested for free hydrochloric acid with Congo red paper and for free and total acidity with Toepfer's solution and phenolphthalein as indicators. If free acid is absent with Toepfer's solution, the pH is 3.5 or higher. Each sample is inspected for the presence of neutral red. This appears as a watery pink to a red color. Rarely in the late aspirations, bile, stained reddish-brown by the dye, regurgitates into the stomach. This can be readily recognized by the experienced eye and possibly vitiates the test somewhat, so that it is better in such instances to repeat the procedure. If no free acid is present, each sample may be acidified to bring out the dye. If the dye appears and free acid does not (and this is a very important point) it signifies in our experience, that the stomach is capable of secreting free acid, that the achlorhydria is a temporary or false one (inhibition, insufficient stimulation, or, neutralization of the free acid) and that further tests are indicated. Under such conditions it has been our custom to repeat the test meal with certain modifications. The histamine, provided the reaction to 0.5 mg. was slight, may be increased to 1 mg. The patient is given one-half of an orange to chew and directed to expectorate all the pulp and juice, *i. e.*, a powerful psychic stimulus, and finally warm bouillon or 5% alcohol (75 cc.) is added to the oatmeal gruel meal. The last provide a very strong chemical stimulus. If such a meal fails to reveal free hydrochloric acid, the large Ewald tube may be passed unexpectedly 1 or 2 hours after the patient has eaten his usual meal (breakfast or dinner) at home or on the ward. In this way we have found (see below) that when neutral red appears within the period of the 2-hour test meal, that the stomach is capable of secreting free acid and that we are not dealing with a true achlorhydria. We have concluded as a result of these studies that histamine alone is not sufficient to establish the diagnosis of true achlorhydria.

Material. A routine Rehfuß fractional test meal (150 cc. strained oatmeal gruel with $\frac{1}{4}$ hour aspirations for 2 hours) was carried out in 5585 consecutive patients in the Gastro-Intestinal Clinic at the Mount Sinai Hospital. Whenever a 2-hour achlorhydria was encountered the combined test described above was instituted.

Results. In 5585 consecutive cases we encountered 117 cases of true achlorhydria (2.2%). If the cases of pernicious anemia, gastric carcinoma, partial gastrectomy, gastric syphilis, chronic gall bladder disease, and Graves' disease, comprising in all 46 examples of diseases usually associated with achlorhydria, are excluded, 69 instances of true achlorhydria of undetermined etiology are left.

This is an incidence of 1.2% in 5585 consecutive test meals obtained from a group of miscellaneous patients attending the Gastro-Intestinal Clinic. In these 69 true achlorhydrias a trace of pepsin was found in all but 2 cases. Complete blood studies are not at hand in all of these cases. Of 11 who were studied hematologically, 8 had a hemoglobin between 85% and 100% and a red cell count of $4\frac{1}{2}$ to 5 millions. Two patients had a mild secondary anemia and 1 had a severe microcytic secondary anemia (45% hemoglobin and $2\frac{3}{4}$ million red blood cells).

The distribution in the sexes and in the different age levels of our cases of true achlorhydria unassociated with definite organic diseases is given in Table I. It is interesting to note that the incidence in males is greater. In view of the fact that an analysis of the total

TABLE 1.—ANALYSIS OF THE CASES OF TRUE ACHLORHYDRIA OF UNDETERMINED ETIOLOGY.

Age.	Male.	Female.	Cases.
0-20	1	1	2
20-30	2	5	7
30-40	5	6	11
40-50	15	6	21
50-60	9	5	14
60-70	10	4	14
Total	42	27	69

number of male and female cases studied was not made, the statistical significance of this sex difference cannot be established. The fourth, fifth and sixth decades show nearly double the number of cases in the first three decades. The extremely small incidence of true achlorhydria of unknown etiology in our series is indeed striking. It is our impression from prolonged observation of some of these cases, that despite intensive therapy, the free acid rarely returns.

We were dissatisfied with the methods and studies reported when we found in our studies that when neutral red is excreted into the stomach after intramuscular injection, irrespective of whether free acid appears in that test or not, the stomach is capable of secreting free acid and with some modification of the test meal will do so sooner or later. That our ideas in this respect were correct was proved by our experience in 15 cases where histamine ($\frac{1}{2}$ to 1 mg.) plus neutral red plus oatmeal gruel was used as a combined test and neutral red appeared without the presence of free hydrochloric acid. In each instance, at a subsequent test of one type or another, free hydrochloric acid was demonstrated. This is a striking point and possibly invalidates conclusions which have been drawn from "histamine achylia." Apparently, neutral red is a more delicate indicator of the functional activity of the gastric secretory cells than histamine.

Comment. It is apparent, if one excludes the diseases associated with true achlorhydria, that this affection of the stomach is indeed

a rare one. The obvious deduction is that when a physician encounters a patient with a true achlorhydria, it is often associated with a definite disease and it is, therefore, imperative that he search intensively for one of the usual underlying causes or conditions. Whether the patients who do not reveal an associated disease will develop one of these diseases, particularly one of the anemias or carcinoma, as Hurst suggests, depends on a survey of the entire situation. We watch particularly for the onset of pernicious anemia, gastric carcinoma, and gastritis. A history of pernicious anemia or unexplained secondary anemia in other members of the family, familial achlorhydrias, burning sensation in the tongue or objective glossitis, dysphagia, paresthesiæ, lemon-yellow color, subicterus, diarrheas, pallor, weakness, or evidence of spinal cord involvement, should suggest the possibility of pernicious anemia, present or impending. Loss of strength, anorexia, aversion for certain foods, loss of weight, nausea, constipation and anemia should evoke at once the thought of carcinoma. A mild, chronic gastritis without anemia or carcinoma gives, as a rule, no or only mild symptoms. However, epigastric pain, fullness and pressure immediately on and after eating; morning nausea, heartburn, belching; constipation or diarrhea or an alternation of these symptoms; vague diffuse abdominal pain; flatulence and cramps may follow or be reflected from a diffuse inflammation of the gastric mucosa. It seems therefore advisable to watch the stomach of these patients for the changes which give evidence of inflammation, namely, an increase in mucus, hypertrophy of the rugæ in the radiographic examination and certain gastroscopic changes (chiefly atrophy and hypertrophy). It is probable that the near future will reveal an improvement in the diagnosis of chronic gastritis because of increasing skill in gastroscopic methods. Schindler, Moutier, Jackson and others have reported characteristic gastroscopic pictures in chronic gastritis.

It seemed of interest and importance to gastroscop the stomachs of some patients with true achlorhydria of undetermined etiology. Fourteen patients were selected for study.* Summarizing the table, 9 of the patients (64%) showed a diffuse atrophic gastritis; 4 showed a hypertrophic gastritis; in 2 of these the lesions were diffuse and in 2 were located in the antrum; in 1 there was a mixed hypertrophic and atrophic gastritis diffusely located. It is apparent that a severe gastritis was present in all of these true achlorhydrias; none was normal. It is of interest that in two-thirds of the cases there was a diffuse atrophic gastritis. *A priori*, one would expect this type of gastritis to be associated with true achlorhydria. Whether it is associated with the development of carcinoma as suggested by Schindler and Hurst will only be answered by careful future studies.

* I am indebted to Drs. Rudolph Kramer and Henry Lerner for the data obtained in these examinations (see Table 2).

This brief study also suggests but, of course, does not prove, that the advanced gastritis noted in most of the patients probably preceded and caused the true achlorhydria.

TABLE 2.—GASTROSCOPIC FINDINGS IN TRUE ACHLORHYDRIA.

Case.	Type of gastritis.			Location of gastritis.		
	Atrophic.	Hyper-trophic.	Mixed.	Antrum.	Fundus.	Diffuse.
1	..	+	..	+		
2	+	+
3	+	+
4	+	+				
5	..	+	..	+	+	
6	..	+				
7	+	+
8	+
9	+	+
10	+	+
11	+	+
12	+	+
13	+	+
14	+	+

Hurst has suggested a prophylaxis of the chronic gastritis associated with the achlorhydric state. In general, from his observations, it would seem advisable in public health work, to advise people from 35 years upward, with or without symptoms, to have a test meal and Roentgen examination and possibly a gastroscopy every 6 to 12 months. Should an achlorhydria or other evidence of gastritis be at hand, one should institute prophylactic and therapeutic measures. For example, diet, gastric lavage (autolavage or by the physician), liver and iron. After some improvement the administration of hydrochloric acid and pepsin may be indicated. While not a cure-all or a perfect prophylaxis, some such plan, Hurst thinks, would possibly, 1, give us earlier diagnoses of pernicious anemia, achlorhydric anemia, gastric carcinoma, chronic gastritis, chronic gall bladder disease, Graves' disease; 2, help to prevent in some measure such anemias as mentioned; 3, cure or retard chronic gastritis and thus, 4, perhaps by decreasing both the atrophic and the hyperplastic reparative phase of the inflammation, lessen somewhat the incidence of gastric carcinoma.

Finally, a few words should be added concerning the etiology of the true achlorhydrias. Hurst⁵ feels that all human stomachs are subject to chronic irritants (dietetic, infectious, traumatic, alcohol, tobacco, and so on) and that 80% endure these insults very well. Ten percent, he believes, will get a "hyperchlorhydric gastritis" which leads to the ulcer disease. Another 10% will develop the subacid or achlorhydric gastritis which may lead to the anemias or to the malignant state. Why these endogenous and exogenous irritants should cause in some patients secretory hyperfunction and in others hypofunction is not clear. Apparently we must fall back with Hurst on the "constitution" idea. While interesting and stimulating, these suggestions require careful study. One demands further

evidence in order to accept this attractive hypothesis. Recently we observed a small group of patients with gastric ulcer with free acid who later developed achlorhydria. This would seem to indicate a progressive gastritis. In other words, the gastritis accompanying ulcer may also lead to the hypochlorhydric state.

Faber⁴ in a recent monograph on gastritis reiterates his belief that achlorhydria is due to gastritis. He disagrees with Hurst in that he explains the hypochlorhydric and hyperchlorhydric states on the basis of a difference in the type, degree, and localization of the gastritis rather than on a constitutional basis.

We are inclined to agree with these authors that gastritis is the chief cause of achlorhydria and that, henceforth, the inflammatory states of the stomach should engage our attention closely. There may be many varied causes for the gastritis. In addition to those suggested by Hurst, it seems probable that certain functional states (pylorospasm, retention, atony, hypertonic states, myospasm, vasospasm, acid-pepsin irritation), and toxic-infectious factors (chiefly from the nose, throat and teeth) may play a very important rôle in the genesis of gastritis. We are at present conducting an investigation of the occurrence and diagnosis of gastritis under these various conditions.

Summary and Conclusions. 1. The terms "anacidity" and "achylia gastrica" should be dropped and "false" or "true" achlorhydria be adopted. By "true" is meant one that is complete, more or less permanent and with a pH of 3.5 or over.

2. The Ewald and Riegel test meals, the oatmeal gruel fractional test meal, or the histamine test alone, are insufficient to establish the diagnosis of a true achlorhydria.

3. A combination test including oatmeal gruel, histamine, and neutral red seems more efficient in the diagnosis of true achlorhydria.

4. Using this procedure, we have found that the incidence of true achlorhydria unassociated with the organic diseases usually accompanying true achlorhydria is very low (1.2%), *i. e.*, true achlorhydria of undetermined etiology is rare in individuals, young or old.

5. Inasmuch as true achlorhydria is often associated with definite organic diseases, its presence should lead the examiner to a thorough search for these diseases.

6. In the absence of such diseases certain prophylactic measures against the gastritis probably causing the achlorhydria should be instituted in an attempt to prevent the subsequent development of these diseases.

7. It is possible that the incidence of pernicious anemia, some of the secondary microcytic anemias, various intestinal disturbances, chronic gall bladder and liver disease, various allergic phenomena, and, above all, gastric carcinoma, may be lessened by the proper study, recognition, and prevention of the gastric inflammatory states which lead to subacidity and the achlorhydrias.

8. Finally, the possible etiologic factors involved in the gastritis associated with achlorhydria are briefly reviewed and discussed.

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IMMEDIATE FEEDING VERSUS INITIAL STARVATION IN THE TREATMENT OF BLEEDING PEPTIC ULCER.

By J. P. EICHHORN, M.D.,

ASSISTANT RESIDENT PHYSICIAN, DEPARTMENT OF INTERNAL MEDICINE, CLEVELAND CITY HOSPITAL, CLEVELAND, OHIO.

(From the Department of Medicine of Cleveland City Hospital and the Western Reserve University School of Medicine.)

THE purpose of this paper is to compare the results of initial starvation followed by a progressive Sippy diet with the Meulengracht regimen in the treatment of 81 patients with bleeding peptic ulcers admitted to this hospital from January 1, 1936, to April 15, 1941, inclusive.

In the majority of these cases, the diagnosis was substantiated by Roentgen-ray, subsequent operation, or autopsy. In only 17 of the 81 cases was the diagnosis a clinical one. No cases were included in which the red blood cell count was not below 4 million. Those cases with concomitant perforation of a peptic ulcer were excluded. Also not included are 6 patients from the Sippy series and 3 patients from the Meulengracht group who were treated by early surgical intervention when they appeared to fail to respond to medical management. One patient died from generalized peritonitis and the others recovered.

Of the 43 patients treated by initial starvation, 37 were males and 26 of the 38 patients who were fed immediately were males. Although males predominate in the former group, there is no reference in the literature to any difference in prognosis between the two sexes. The average age of the patients treated by the Sippy regimen was 44 years and that of the group treated by Meulengracht's method was 46 years. Since the mortality rate rises with increasing age in this disease, the advantage here, though slight, lies with the group treated by the Sippy routine. There were 13 gastric ulcers, 21 duodenal ulcers, and 9 of undetermined location in the patients treated by initial starvation. In the group treated by immediate

feeding the lesions were distributed as follows: gastric, 12; duodenal, 15; marginal, 4; and undetermined location, 8.

Methods. In this hospital, until July of 1939, patients with bleeding peptic ulcers were starved for an initial period averaging 3 days (range 1 to 6 days). They were then started on progressive Sippy diets, often having their food intake further restricted by being kept on the first day Sippy diet for several days. They were given aluminum hydroxide in widely varying dosage. Most of the patients received iron toward the end of their hospital stay. Patients often were given sedatives liberally.

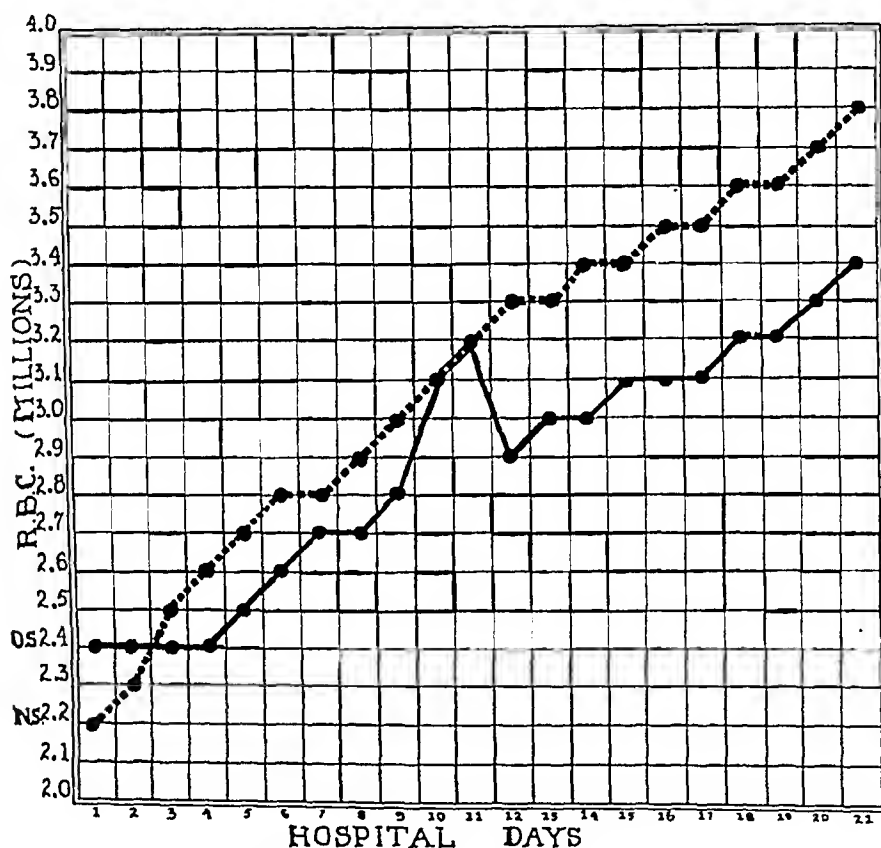


CHART 1.—Average daily erythrocyte count of the patients treated by initial starvation (solid line, O.S.) compared with those treated by Meulengracht's method (broken line, N.S.).

In 1932, Meulengracht^{2a,b} of Copenhagen first advocated the system of treatment which bears his name. Meulengracht, who has never referred a bleeding patient for surgery, believed it to be fundamentally wrong to withhold food and drink from patients in a condition of posthemorrhagic shock. He stated as his reasons for advocating the feeding of these patients, first, that patients often die in spite of rigid diet or the complete withdrawal of food; second, that patients have been observed to stop bleeding and recover from their anemia although they remain ambulatory and do not seek treatment; and lastly, that a diet deficient in vitamins and calories does not promote either the healing of ulcers or the regeneration of blood. In analyzing the results of cases treated by the old method he found that most of them died about the eighth day, which was exactly the average number

of hospital days of the fatal cases in this series. He postulated that many of these patients died from sheer exhaustion. He also pointed out that patients were more comfortable and that the nursing care was easier and the hospital stay shortened when the patients were fed. Other authorities have advanced further reasons for the use of liberal feeding. Lanphere,¹ in particular, emphasized that a high carbohydrate and protein intake tends to protect the liver and to prevent acidosis. Others have suggested that free acid in an empty stomach delays the healing of ulcers.

Of Meulengracht's own series of 491 consecutive patients treated by feeding, only 10 died—1 from perforation of his ulcer, 4 before they could be fed, and 5 from recurrent hemorrhage, giving a corrected mortality of 1%.

Since July, 1939, all patients with bleeding ulcers have been treated with frequent nutritious feedings from the time of admission. Patients who vomit food or blood are refed. The foods are selected by the dietetic staff from a large assortment of vegetables and fruits, all cooked and strained, and each patient is given 100 cc. of orange juice daily for the vitamin C content. Cereals, crackers, wafers, and toasted bread are all allowed and eggs are used freely; prepared in any way except by frying. Meat or fish, which is baked, boiled, or broiled, is given daily from the beginning. The patients are given cream soups, any beverage except coffee, and such desserts as custards, puddings, jello, or ice cream. In addition to their diet these patients received 0.7 gm. of ferrous sulphate 3 times a day and 9 4-cc. doses of aluminum hydroxide in 24 hours. Patients are required to take 3000 cc. of fluid daily. Blood transfusions are given freely when the erythrocytes are under 2 million, when there is evidence of shock, or when the blood urea nitrogen is elevated. Of this group of patients, 23 received an average of 865 cc. of blood. Among the surviving patients treated by initial starvation, 21 were given an average of 790 cc. of blood.

Results. Among the 43 patients treated by initial starvation, 8 died, a mortality rate of 19%. In the second series of 38 patients, treated by immediate feeding, there were no deaths. The graph represents the average daily gain in red blood cells of the two groups of cases, excluding the fatal cases. It will be noted that the patients who were fed at once regenerated blood more rapidly than the survivors among the starved ones. The average period of hospitalization of the earlier series was 29 days, as compared to 25 days for the later series. Three patients had hematemeses during the starvation period and more than 24 hours after admission. None of the patients who were fed on admission vomited blood more than 24 hours after treatment was started.

Conclusion. In a series of 81 patients with bleeding peptic ulcers, 43 were deprived of food and 38 were fed immediately. Comparison of the results in the two series indicates that immediate liberal feeding results in, first, a greatly lowered mortality rate, second, more comfort for the patient, and, finally, a shorter hospital stay.

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BOOK REVIEWS AND NOTICES

AN X-RAY ATLAS OF SILICOSIS. By ARTHUR J. AMOR, M.D. (Lond.), M.Sc. (Wales), Honorary Physician, Clydach Memorial Hospital; Medical Officer, Mond Nickel Company, Ltd., Swansea. With Translation of the Legends into French by ROBERT E. HORNE, M.A. (Wales), Medical Secretary, Mond Nickel Company, Ltd., Swansea. With a Foreword by SIR WILSON JAMESON, M.A., M.D. (Aberdeen), F.R.C.P., of the Middle Temple, Barrister-at-Law; Dean of the London School of Hygiene and Tropical Medicine. Pp. 206; 6 text illustrations and 72 plates. Baltimore: The Williams & Wilkins Company, 1941. Price, \$8.00.

THIS Atlas of Silicosis was written to describe the essential radiologic features of silicosis for senior medical students, industrial physicians, and those dealing with this type of disease.

The author has commented briefly upon etiology, pathology, Roentgen manifestations, and clinical findings in silicosis and some of the nonspecific pneumoconioses. He does not attempt to go into detail concerning many of the aspects of this subject. He has, however, given enough in the first four chapters, which are 30 pages in length, to stimulate one to look elsewhere if interested in this subject. Believing that the average physician is not familiar with the Roentgen findings in a number of these conditions, he has devoted the major portion of his book to illustrating representative chest films with a brief history in both English and French.

The publishers have selected a very good print for this book, but the paper is so glossy that it is exceedingly difficult to read unless light is just right. In selecting a calendar of paper for the illustrations of the roentgenograms of the chest, however, they have done an excellent job. I do not know of any more difficult condition to illustrate than the Roentgen findings in silicosis, and yet in this case the author's attempts have been successful.

E. P.

EPILEPSY AND CEREBRAL LOCALIZATION. A Study of the Mechanism, Treatment and Prevention of Epileptic Seizures. By WILDER PENFIELD, Litt.B., M.D. (Johns Hopkins), D.Sc. (Oxon., Princeton); Professor of Neurology and Neurosurgery, McGill University; Director of the Montreal Neurological Institute, and THEODORE C. ERICKSON, M.A., M.Sc., M.D. (Minnesota), Ph.D. (McGill), Associate Professor of Surgery, University of Wisconsin. Chap. XIV, by HERBERT H. JASPER; Chap. XX, by M. R. HARROWER-ERICKSON. Pp. 623; 163 illustrations. Springfield, Ill.: Charles C Thomas, 1941. Price, \$8.00.

THE leading contributor of this volume is a widely known surgeon who has done original work in epilepsy. In this encyclopedic work, there is comprehensive discussion of the entire subject concerning epilepsy. Epileptic mechanisms are given careful consideration. The chief surgical contribution is the objective treatment of atrophic cerebral lesions, wherein the surgical technique is minutely described. The cerebral cortex of conscious subjects is observed and the epileptic pattern discharge described. Roentgenology considers the atrophic lesions of the brain and skull. A long chapter is electroencephalography, where it is said to be, "(a) an aid to diagnosis of epilepsy and allied conditions, (b) a means of classification (c) a

guide to medical or surgical therapy, (d) a means of observing subclinical cerebral disorders, (e) an aid to discovery of cerebral disorders allied to those of epilepsy in patients without clinical epilepsy but with migraine, mental disease, behavior difficulties, etc., and, (f) an aid in estimating the rôle of heredity in epilepsy." The most useful drugs, phenobarbital, dilantin and the bromides are given careful consideration. Among other subjects, epileptic psychology considers the important psychic seizures. The treatment of acute head injuries is well discussed, and vastly important, is the prevention of post-traumatic epilepsy. This volume is of consequence, more so than any we know of on this subject. As for the publishing, it is a triumph of art.

N. Y.

PATHOLOGY OF THE ORAL CAVITY. By LESTER RICHARD CAHN, D.D.S., Associate Professor of Dentistry (Oral Pathology), Columbia University, etc. Pp. 240; 165 illustrations. Baltimore: The Williams & Wilkins Company, 1941. Price, \$5.50.

THIS is a text on the special pathology of a selected group of more or less common diseases of the mouth. It is chiefly morphologic, while pathogenesis and etiology are sketchily or slightly mentioned. Some diseases are adequately treated; others are presented in an unsatisfactory fashion. For instance, dental caries is described in less than 4 pages, 2 of which are filled with 4 photomicrographs, while the comparatively rare odontomata and ameloblastomata have been given more than 13 pages, including 15 illustrations. Though the text presents little that would make the book commendable to dentists or dental students, the Reviewer wishes to praise the illustrations, some of which are of superb quality.

W. E.

DISEASES OF THE BLOOD and Atlas of Hematology. With Clinical and Hematologic Descriptions of the Blood Diseases Including a Section on Technic and Terminology. By ROY R. KRACKE, M.D., Professor of Bacteriology, Pathology and Laboratory Diagnosis, Emory University School of Medicine; Pathologist to the Emory University Hospital, etc. Pp. 692; 46 text illustrations and 54 color plates. Second Edition, thoroughly revised, reset and enlarged. Philadelphia: J. B. Lippincott Company, 1941. Price, \$15.00.

It is a healthy sign for English-speaking hematology that a book of this size and cost should require a second edition in 4 years. As the first edition was not reviewed in these columns we now present for our readers a lengthier notice than is customary for a second edition.

The book is large because it covers both clinical and laboratory phases of a large and rapidly expanding subject. But it is essentially practical, differing chiefly from Downey's "System" in giving but little space to theoretical considerations. Even such hoary but important controversies as that of the origin of blood cells are presented chiefly on a factual basis, briefly but concisely, as of practical importance to the clinical hematologist. Here, incidentally, the "trialist" theory is offered not because it is the author's preference, but as that most widely accepted. This avoidance of all but the immediately "practical" produces, necessarily perhaps, such regrettable omissions as the valuable non-morphological data on blood cells that have been obtained by the study of living cells (the Lewises, McCutcheon and Coman, and others).

To the contributors to the first edition (J. J. Clark, F. P. Parker, Elizabeth Gambrell—all of Emory University—and R. P. Custer—University of Pennsylvania) has now been added Lloyd Craver, of the Memorial Hospital

of New York. The name of Hortense Garver, co-author of the first edition, no longer appears on the title page.

The book is divided into 8 sections: Hematologic Terminology (40 pages); Development and Morphology of Blood Cells (60 pages); Leukocytosis and Leukopenia (49 pages); the Anemias (193 pages); the Leukemias (66 pages); Hemorrhagic Diseases (34 pages); Miscellaneous Conditions (121 pages); Hematologic Technic (81 pages). Thus, the arrangement is on a "practical" basis rather than in a logical sequence, but well proportioned—the anemias and leukemias occupying more than half the book.

In the first section the pages wisely devoted to terminology permit the student to start from a firm basis. Some novel terms are recommended, preceded by a table of term origins. Most of these (*e. g.*, neutrocytosis, neutropenia, fragilocyte, crenocyte) are distinctly advantageous, to avoid more cumbersome though perhaps etymologically more correct terms. In other cases, as good usage never can be entirely consistent, the older term seems preferable. "Basocyte," for instance, has no advantage over "basophil," which not only has the recommendation of long usage, but also expresses the cell's qualities more accurately; the same with "neutrophil" and "eosino- (acido-)phil."

As far as the Reviewer has been able to determine, all the sections are uniformly good. A pathologist would naturally like more on pathologic anatomy as illuminating the disease processes, but this is hardly to be expected in view of the author's expressed aims.

The illustrations are good (on heavy coated paper) and well explained. Cell magnifications are not given, so that one has to rely on the general statement that they are mostly about 1200 diameters. Anyone desiring but one volume on Hematology would do well to make this the one.

E. K.

EYE HAZARDS IN INDUSTRY. Extent, Cause, and Means of Prevention.

By LOUIS RESNICK. Pp. 321; 33 illustrations. New York: Columbia University Press, 1941, for National Society for the Prevention of Blindness. Price, \$3.50.

THIS is an excellent book for the layman on the prevention of eye injuries in industry. It is written by a man who has obtained his information first-hand in factories and work shops where ocular injuries are frequent. It does not pretend to be a medical book describing eye injuries, although there is a chapter giving in lay terms the type of injuries and diseases met with. This is perhaps the weakest part of the book.

It is to be recommended to all Social Service workers, hospital authorities, large industrial concerns, and insurance companies, and could be read with profit by every foreman in a factory.

F. A.

THE PROCEEDINGS OF THE CHARAKA CLUB. VOLUME X. "Post Multa Virtus Opere Laxare Solet." Pp. 260; illustrated. Baltimore: The Williams & Wilkins Company, 1941, for The Charaka Club. Price, \$5.00.

IN the same vein as in previous volumes, this Volume X presents selections from the cultural essays of its members during the past 4 years. Various tastes are served. Some idea of the range covered may be had from such titles as Packard's "Fig Leaves for Shakespeare and Montaigne," Steiner's "Story of Barbara Fritchie," Wortis' "We All Have a Word for It," Whipple's "Ramblings of a Rug Addict," Rake's "An Early Pill Slab and the Lambeth Potters," Lund's essays on Galen and Aulus Gellius. Sachs' "Early Years of the Charaka Club" gives a good picture of this interesting organization.

E. K.

DISEASES OF WOMEN. By HARRY STURGEON CROSSEN, M.D., F.A.C.S., Professor Emeritus of Clinical Gynecology, Washington University School of Medicine; Gynecologist to the Barnes, St. Louis Maternity and St. Luke's Hospitals, etc., and ROBERT JAMES CROSSEN, A.B., M.D., Assistant Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine; Assistant Gynecologist and Obstetrician to the Barnes and the St. Louis Maternity Hospitals, etc. Pp. 948; 1127 illustrations, many in color. Ninth Edition, entirely revised and reset. St. Louis: The C. V. Mosby Company, 1941. Price, \$12.50.

THE Ninth Edition of this classic text, "Diseases of Women," had undergone considerable revision to include the advances of this science in the 6 years which have elapsed since the last edition. There have been added 145 illustrations, many in color. No details of operative gynecology are given in this book as they are contained in the companion book on "Operative Gynecology" by the same authors.

Since the major investigative interest in gynecology has shifted in recent years to the physiologic aspect of the subject, it is but natural that a revision should take place, and much new material has been added to the discussion of hormones and endocrine activities. What is useful in these advances has been offered in such a way that the practicing physician may employ them in his daily work. The book will hold the same high mark in gynecological literature attained by its predecessors. P. W.

SEX LIFE IN BABYLONIA. By EDWIN W. HIRSCH, M.D. (From the Urologic and Cutaneous Review, September, 1941.) Pp. 38. Chicago: Research Publications, 1941.

THIS booklet contains matter, reprinted from the Urologic and Cutaneous Review (Sept., 1941), by the author of "The Power to Love" and "Feel Like Thirty at Fifty." It purports to be the first of a series "to help the sexually blind see clearly the issues of life" by studying the sexual life, customs and laws of various peoples. It is written in an unscientific style that includes inaccuracies such as attributing the loss of the Babylonian civilization to the Flood so graphically described in the Bible. Attitudes toward sexual intercourse and demonic influences that were widespread among primitive and early races are naively offered as special qualities of the Babylonians and quite unjustifiable inferences are made to show that they were aware of syphilis, for instance. The surprising opening statements that "more people die from fear than from any other single cause . . . the most deadly form is sexual fear" receive neither explanation nor support in the rest of the text. E. K.

DISEASES OF THE THYROID GLAND. Presenting the Experience of More than Forty Years. By ARTHUR E. HERTZLER, M.D., Surgeon to the Halstead Hospital; Professor of Surgery in the University of Kansas. Pp. 670; 354 illustrations and 2 colored plates. New York: Paul B. Hoeber, Inc., 1941. Price, \$8.50.

THROUGHOUT this book there is repeated again and again the following conviction that *total* thyroidectomy should be done for all types of goiters observed after adolescence: ". . . it seemed logical to remove totally goitrous glands in adults, both plus and minus, and the indications, based on experience, are that both states are thus eliminated. In other words myxedema, like hyperthyroidism, is due to some deleterious secretion and not to a cessation of a normal function as commonly believed." As an

example of the literary style, may be cited the following: "It is first of all to be realized that the term myxedema is not synonymous with deficient thyroid secretion. This belief has been one of the sacred cows in medicine and any one who made merry with the old bossie did so at his peril, but the old critter has gone to the hamburger factory for ignominious extinction."

The author intends this to be a personal record of his 40 years' experience in thyroid surgery, and not as a treatise on thyroid disease. Even so, it does not impress the reader that the author has deep knowledge or unbiased good judgment when he does not discuss our present knowledge of iodine metabolism and ignores or ridicules nearly every one's views except his own. There is no bibliography. Many statements on physiology and microscopic pathology are not sound.

The text is not worthy of the very beautiful physical make-up of the book. I. Z.

THE MARCH OF MEDICINE. New York Academy of Medicine Lectures to the Laity, 1941. Pp. 154; 4 illustrations. New York: Columbia University Press, 1941. Price, \$2.00.

THE Lectures to the Laity of the New York Academy of Medicine are filling a great need in this day when the laity devour with eagerness every scrap of information on medicine to which they have access. These lectures on very varied medical topics of great importance at the present time, are all delivered by recognized authorities on the subjects which they discuss. While dealing with the deepest scientific material the lecturers present it in a way which not only renders the subject readily comprehensible to a lay audience but excites deep interest in the hearers. F. P.

NEW BOOKS.

The Blood Bank and the Technique and Therapeutics of Transfusions. By ROBERT A. KILDUFFE, A.B., A.M., M.D., F.A.S.C.P., Director, Laboratories, Atlantic City Hospital; City Bacteriologist, Atlantic City; Serologist, Municipal Hospital for Contagious Disease, Atlantic City, etc., and MICHAEL DE BAKEY, B.S., M.D., M.S., F.A.C.S., Assistant Professor of Surgery, School of Medicine, Tulane University of Louisiana; Visiting Surgeon, Charity Hospital, Touro Infirmary, and Merey Hospital, New Orleans, etc. Pp. 558; 214 illustrations. St. Louis: The C. V. Mosby Company, 1942. Price, \$7.50.

A Primer on the Prevention of Deformity in Childhood. By RICHARD BEVERLY RANEY, B.A., M.D., Associate in Orthopaedic Surgery, Duke University School of Medicine, Durham, N. C.; Attending Orthopaedic Surgeon, Watts Hospital, Durham, N. C. In Collaboration with ALFRED RIVES SHANDS, JR., B.A., M.D., Medical Director, Alfred I. duPont Institute of The Nemours Foundation, Wilmington, Del.; Visiting Professor of Orthopaedic Surgery, University of Pennsylvania School of Medicine, Philadelphia. Pp. 188; 88 illustrations by JACK WILSON. Elyria, Ohio: National Society for Crippled Children, Inc., 1941. Price, \$1.00.

Psychosurgery. Intelligence, Emotion and Social Behavior Following Pre-frontal Lobotomy for Mental Disorders. By WALTER FREEMAN, M.D., Ph.D., F.A.C.P., Professor of Neurology, George Washington University, and JAMES W. WATTS, B.S., M.D., F.A.C.S., Associate Clinical Professor of Neurosurgery, George Washington University, Washington, D. C. With special psychometric and personality profile studies by THELMA HUNT, M.D., Ph.D., Associate Professor of Psychology, George Washington University, Washington, D. C. Pp. 337; 81 illustrations. Springfield, Ill.: Charles C Thomas, 1942. Price, \$6.00.

- Neuroanatomy.* By FRED A. METTLER, A.M., M.D., Ph.D., Professor of Anatomy, University of Georgia, School of Medicine, Augusta. Pp. 476; 337 illustrations (30 in color). St. Louis: The C. V. Mosby Company, 1942. Price, \$7.50.
- The Medical Clinics of North America, Vol. 26, No. 1* (Chicago Number, January, 1942). Pp. 313; 45 illustrations. Philadelphia: W. B. Saunders Company, 1942.
- Clinical Roentgenology of Pregnancy.* By WILLIAM SNOW, M.D., Director of Radiology, Bronx Hospital; Roentgenologist-in-Charge, Harlem Hospital, New York City. Pp. 178; 119 illustrations. Springfield, Ill.: Charles C Thomas, 1942. Price, \$4.50.
- Laboratory Diagnosis of Protozoan Diseases.* By CHARLES FRANKLIN CRAIG, M.D., M.A. (Hon.), F.A.C.S., F.A.C.P., Colonel, United States Army Medical Corps, Retired, D.S.M.; Emeritus Professor of Tropical Medicine, Medical School, Tulane University, etc. Pp. 349; 54 illustrations and 4 colored plates. Philadelphia: Lea & Febiger, 1942. Price, \$4.50.
- Four Treatises of Theophrastus von Hohenheim Called Paracelsus.* By C. LILIAN TEMKIN, GREGORY ZILBOORG, GEORGE ROSEN, HENRY E. SIGERIST. Edited, with a Preface by HENRY E. SIGERIST. Translated from the original German, with Introductory Essays. Pp. 256; 1 illustration. Baltimore: The Johns Hopkins Press, 1941. Price, \$3.00.
- Clinical Hematology.* By MAXWELL M. WINTROBE, M.D., Ph.D., Associate in Medicine, Johns Hopkins University; Associate Physician, Johns Hopkins Hospital; and Physician-in-Charge, Clinic for Nutritional, Gastro-Intestinal and Hemopoietic Disorders, Baltimore. Pp. 792; 167 illustrations and 7 colored plates. Philadelphia: Lea & Febiger, 1942. Price, \$10.00.
- Source Book of Medical History.* Compiled with notes by LOGAN CLENDENING, M.D., Professor of the History of Medicine, University of Kansas. Pp. 685. New York: Paul B. Hoeber, Inc., 1942. Price, \$10.00.

NEW EDITIONS.

- A Text-Book of Neuro-Anatomy.* By ALBERT KUNTZ, Ph.D., M.D., Professor of Micro-Anatomy in St. Louis University School of Medicine. Pp. 518; 307 illustrations. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1942. Price, \$6.00.
- A Hand-Book of Ocular Therapeutics.* By SANFORD R. GIFFORD, M.A., M.D., F.A.C.S., Professor of Ophthalmology, Northwestern University Medical School, Chicago; Attending Ophthalmologist, Passavant Hospital, Wesley Memorial Hospital, Cook County Hospital. Pp. 410; 69 illustrations. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1942. Price, \$4.00.
- Food and Beverage Analyses.* By MILTON ARLANDEN BRIDGES, B.S., M.D., F.A.C.P., Late Director of Medicine, Department of Correction Hospitals, New York; Consulting Physician, Scaview Hospital, Staten Island, New York, etc., and MARJORIE R. MATTICE, A.B., M.S., Assistant Professor of Pathological Chemistry, Department of Medicine, New York Post-Graduate Medical School, Columbia University; Chief Chemist, New York Post-Graduate Hospital, etc. Pp. 344. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1942. Price, \$4.00.
- Science and Sanity.* An Introduction to Non-Aristotelian Systems and General Semantics. By ALFRED KORZYBSKI, Director, Institute of General Semantics. Pp. 798; illustrated. Second Edition with Supplementary Introduction and Bibliography. Chicago: The International Non-Aristotelian Library Publishing Company, 1941. Price, \$6.00.

PROGRESS OF MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF

G. LYMAN DUFF, M.A., M.D., Ph.D.

STRATHCONA PROFESSOR OF PATHOLOGY, MC GILL UNIVERSITY,

AND

E. G. D. MURRAY, O.B.E., M.A., L.M.S.S.A., F.R.S.C.

PROFESSOR OF BACTERIOLOGY AND IMMUNITY, MC GILL UNIVERSITY,
MONTREAL, CANADA.

THE PATHOLOGY OF ISLET CELL TUMORS OF THE PANCREAS.

TUMORS of the pancreas possessing a histologic structure closely resembling that of the islets of Langerhans have been recognized for nearly 40 years. Credit for the earliest clear description of an islet cell tumor belongs to Nicholls,⁴⁹ who in 1902 reported from this Department an example of "simple adenoma of the pancreas arising from an island of Langerhans." A few reports of similar benign tumors followed in subsequent years, but Shields Warren,^{64a} who reviewed the literature in 1926, could find a total of only 16 cases of adenoma of the islets of Langerhans to which he added 4 new cases of his own. Such isolated reports stirred only an academic interest since it was believed, as Warren remarked, that these tumors "probably never give rise to trouble during life and have no clinical significance." With the discovery of insulin in 1922³ and the recognition of insulin shock,^{4,21} there came the realization that oversecretion of insulin might occur and might produce a recognizable clinical syndrome. This idea was crystallized in Seale Harris's concept of "hyperinsulinism."³⁰ However, the possibility that hyperinsulinism and hypoglycemia might occur as the result of secretory activity on the part of an islet cell tumor was first brought to general attention in 1927 by the report of Wilder, Allan, Power and Robertson⁶⁹ of a case in which a carcinoma of the pancreas of islet cell type had produced such effects. Two years later, a case was reported by Howland, Campbell, Maltby and Robinson³² in which "dysinsulinism" was cured by the surgical removal of an islet cell tumor of the pancreas. Since that time there has been a mounting interest in such tumors and in the clinical syndrome which some of them produce. The total number of reported cases recognized either

clinically or at autopsy now exceeds 100, and successful treatment has become almost commonplace. The clinical aspects of hyperinsulinism and hypoglycemia have been carefully reviewed by Sigwald,⁵⁸ Wauchope,⁶⁵ Womack,⁷² Whipple and Frantz,⁶⁸ and others. Whipple and Frantz⁶⁸ in 1935, Whipple⁶⁷ in 1938, and Frantz²² in 1940 included in their papers excellent tabulations of the clinical manifestations and pancreatic lesions observed in the cases reported up to the dates of publication. Isaji³⁴ included a brief résumé of the pathology of islet cell tumors with his report of 2 cases, but so far as the Reviewer is aware, there have been no other attempts to bring together the accumulated information regarding the pathologic features of islet cell tumors of the pancreas.

From the clinical or functional point of view, islet cell tumors fall naturally into two groups: those which produce the hypoglycemic syndrome and those which do not. Anatomic and histologic studies, however, have failed as yet to provide any criteria which permit histologic differentiation of these two groups, so that the pathologist can only classify such tumors as benign or malignant. This distinction has obvious clinical importance, but it has no significance in relation to the possible endocrine activity of these tumors for both the benign and malignant types in some instances produce the hypoglycemic syndrome and in other instances do not. In the absence of clinical evidence of hyperinsulinism or dysinsulinism, islet cell adenomata usually remain unrecognized until discovered at autopsy, while islet cell carcinomata produce a clinical picture which cannot be distinguished from that of any other type of pancreatic carcinoma. Consequently, clinical interest in these tumors depends almost entirely on the ability of some of them to disturb carbohydrate metabolism. Nevertheless, a consideration of islet cell tumors from the pathologic point of view necessitates inclusion of all of them, whether or not they have displayed evidence of functional activity.

For purposes of description and discussion, it is convenient to separate benign and malignant tumors, though it is not an easy separation to make. It is true that some islet cell tumors grow rapidly, invade, metastasize and are obviously malignant. Others are relatively small, grow slowly and lack metastases. However, in certain cases of the latter group the histologic finding of interruption or invasion of the capsule, or even invasion of blood channels by tumor cells, has led those who have reported such cases to doubt that the tumor in question was completely benign. Tumors of this kind have been reported as carcinomata of low grade of malignancy, or as slow-growing carcinomata, or as adenomata, with the question of possible malignancy left in abeyance. Up to the present time the evidence is in favor of the view that these tumors, in spite of their histologic appearance of malignancy, behave as benign growths. In all instances in which an autopsy was obtained, metastases from such tumors were lacking, and in all patients who have survived surgical excision, periodical observation has failed to reveal any sign of recurrence for periods up to 12 years. For the time being, therefore, there is scarcely sufficient reason to create a third category to accommodate these questionable tumors and there is some justification for grouping them tentatively with those which are clearly benign.

Islet Cell Adenoma. *Incidence.* Although Warren^{64a} in 1926 found only 16 cases of islet cell adenoma of the pancreas reported in the previous literature, he expressed the opinion that more careful search of the pancreas at autopsy would reveal a higher incidence than that suggested by the then available figures. This view is vindicated by the findings of Pappenheimer⁵² who discovered islet cell adenomata in 5 of 4010 consecutive autopsies. In 4 of these cases the pancreatic tumor was an incidental finding and in only 1 had there been clinical symptoms. Probably on the basis of these figures, Campbell, Graham and Robinson¹² stated that the incidence of islet cell adenomata was 1 in 800 or 1000 autopsies but that related hypoglycemic symptoms had been encountered in only 20% of cases. As Whipple⁶⁷ has pointed out, "these islet tumors are small, seldom exceeding 1.5 cm. in diameter, and are easily overlooked unless serial sections are made of the pancreas." It is, therefore, entirely possible that the true incidence may exceed even that indicated by Pappenheimer's data. That islet cell adenomata may occur in animals other than man is shown by Hueper's description³³ of an islet adenoma in the pancreas of a white mouse and the report of Slye and Wells⁵⁹ of the finding of multiple benign and malignant islet cell tumors in a dog which had shown evidence of hypoglycemia for 2 years before its death.

Taking together all human cases of islet cell adenoma, whether accompanied by clinical symptoms or not, it is found that the incidence is somewhat higher in males than in females. Among 90 reported cases analyzed by the Reviewer, there were 51 males and 39 females. The male preponderance, however, existed entirely among the 64 cases in which there were clinical symptoms of hypoglycemia; of these, 38 were males and 26 females. Among the 26 cases without hypoglycemic symptoms, males and females were equal in number.

Islet cell adenomata have been found in patients of every decade from the first to the ninth. In about one-half of the 90 cases analyzed the patients were between the ages of 30 and 50 years. However, when one separates the cases with hypoglycemic symptoms from those in which such symptoms were lacking, it is found that the lower age groups are filled almost exclusively by patients who suffered from symptoms of hypoglycemia. Twenty of the 90 patients were under 30 years of age and of these only 3 in the third decade showed no clinical evidence of hyperinsulinism. Hypoglycemia due to islet cell adenomata has been reported in children of 7 and 10 years of age,^{29,71} but it scarcely ever occurs over the age of 60. One case of hypoglycemia due to islet cell adenoma has been reported in a woman 63 years of age,³⁴ but the remaining 10 cases of islet cell adenoma in patients over the age of 60 lacked symptoms of hypoglycemia. The oldest patients in this group were 2 males, each 84 years of age.^{38,56}

The predominant incidence of the hypoglycemic syndrome in association with islet cell adenomata in the earlier age groups and its virtual absence in the later age periods is probably explained, at least in part, by the fact that the clinical manifestations of hypoglycemia invite surgical exploration of the pancreas with the possibility of early discovery of a tumor; or, treatment failing, the pathologist is likely to be given an early opportunity and the stimulus to search the pancreas carefully at autopsy and perhaps to find an islet cell tumor small enough

to have been overlooked in routine examination. On the other hand, non-functioning islet cell adenomata, even though they may originate in the same age periods, are compatible with survival to a ripe old age.

Gross Pathology. While it is true, as is frequently stated, that the most frequent location of islet cell adenomata is in the tail of the pancreas, the surgeon and pathologist must bear in mind that about 25% of these adenomata occur either in the head or at the junction of the head and body of the pancreas. The remainder are distributed in various parts of the body of the pancreas as well as in the tail. It is also of importance to the surgeon that 2 or more islet cell tumors may be present at different places in the same pancreas. Multiple adenomata have been found in about 12% of cases. In more than one-half of these cases there were 2 adenomata, but as many as 5 were found in a case described by Kalbfleisch,³⁷ there were no less than 10 in Lloyd's case,⁴⁴ and great numbers of small adenomata were distributed throughout the whole pancreas in the cases reported by Lang⁴² and Terbrüggen.⁶¹

Islet cell adenomata occur as circumscribed, spherical, ovoid or irregularly rounded masses of variable size. The smallest have been encountered at autopsy in patients who have shown no clinical evidence of hypoglycemia. Warren^{64a} described one adenoma which was only 1.2 mm. in greatest diameter and in his 3 other cases the tumors did not exceed a diameter of 9 mm. However, adenomata of much larger dimensions up to 13 cm. in diameter^{15,43} have been discovered at operation or at autopsy in the absence of any clinical record of signs or symptoms of hypoglycemia. On the other hand, the hypoglycemic syndrome has not been observed in association with islet cell adenomata of a diameter less than 1 cm. In the great majority of instances, the tumors have measured between 1 and 2 cm. in diameter^{67,68} but there have been reported a few cases of hypoglycemia occurring in association with larger islet cell adenomata measuring up to 11 cm.⁵¹ or even 15 cm.¹¹ in greatest diameter.

In gross appearance, islet cell adenomata are nearly always described as being sharply circumscribed and discrete, in some instances showing gross encapsulation. In the living patient they present a pink, reddish-gray or cyanotic color contrasting with the paler yellow color of the surrounding pancreatic tissue. The surface of the tumor may be covered by a rich vascular network. These features are well illustrated in the colored plate published by Whipple and Frantz.⁶⁸ Some degree of redness or cyanotic discoloration usually persists in the fresh surgical or autopsy specimen and the cut surface of the tumor may show a degree of vascularity evidently greater than that of the surrounding pancreas. The tissue composing the nodule is quite homogeneous in appearance and lacks the lobulation of normal pancreatic tissue.⁶⁰ Such tumors are generally somewhat firmer than the pancreatic tissue in which they lie, but they may be soft enough to be difficult to detect by palpation alone when they are buried in the substance of the pancreas.

The progress of fibrosis, hyalinization and finally calcification in some adenomata modifies the color and consistency of these tumors. Depending upon the degree to which these changes have developed there may be a grossly visible increase in connective tissue with a concomitant increase in firmness up to stony hardness. The increase in connective tissue becomes grossly apparent with thickening of the

capsule and the formation of gray trabecular fibrous bands connected with the capsule and traversing the darker tissue of the nodule; or, the tumor may give the impression of complete hyalinization presenting a homogeneous pearly white cut surface resembling that of a hard fibroma. Calcification may or may not be obvious in the gross specimen. The development of marked degenerative changes evidently does not cause cessation of functional activity, for such changes have been repeatedly described in adenomata, the excision of which had effected a clinical cure of the signs and symptoms of hypoglycemia.^{34,40,51,58} Moreover, there is no authentic example of spontaneous cure occurring as the result of degenerative changes in an islet cell adenoma. In an interesting case reported by Herrmann and Gius³¹ hypoglycemic symptoms were relieved by the excision of a calcified mass embedded in the head of the pancreas. While it seems probable that this mass represented an almost completely calcified islet cell adenoma, no islet tissue could be identified in or around the mass to establish this diagnosis.

Histologic Structure. Unless an extract possessing the properties of insulin is obtained from the tumor, the recognition of an islet cell adenoma depends entirely upon the histologic resemblance of the tumor tissue to normal or hyperplastic islands of Langerhans. Most of the reports of individual cases have been accompanied by adequate descriptions of the histologic structure of the tumor in question, but histopathologic studies as such have been relatively few within recent years, comprising only those of Warren,^{64a} Smith and Seibel,⁶⁰ O'Leary and Womack,⁵¹ Laidlaw⁴⁰ and Isaji.³⁴

Warren^{64a} laid down histologic criteria for the identification of islet cell adenomata. The first of these was that the morphology and arrangement of the cells must resemble those of the islands of Langerhans. He required also that the mass should measure at least 1 mm. in diameter and that there should be a definite capsule with compression of the adjacent pancreatic tissue. The presence of a definite fibrous capsule is of special importance in distinguishing very small adenomata from hyperplastic islands of Langerhans which may reach a diameter of 1.5 mm. in some cases of diabetes. However, in many islet cell adenomata of larger size the fibrous encapsulation of the nodule is incomplete.^{22,40,51,58,73} Compression of the neighboring pancreatic tissue is commonly observed but is not always present.^{32,50,58}

Practically all histologic descriptions emphasize the resemblance between the arrangement of the cells in islet cell adenomata and that found in normal islet tissue. O'Leary and Womack⁵¹ and, more recently, Laidlaw⁴⁰ have pointed out that there is a tendency in the formation of islet cell adenomata toward repetition on a large scale of the normal structural relations of the islands of Langerhans. The characteristic feature of the normal pattern is the disposition of the cells in short anastomosing cords, 1, 2 or sometimes 3 cells thick, separated by capillary channels with which they are in very intimate relation. The capillaries are extremely thin-walled, being accompanied only by a delicate network of argyrophil reticular fibers and occasional tenuous strands of connective tissue.

This arrangement of the normal island of Langerhans is almost exactly reproduced in some of the islet cell adenomata,^{40,51} but in most instances certain features of the normal pattern are exaggerated.

Instead of narrow cords of cells, there may be broad irregular bands many cells thick, or rounded clusters of cells, bounded by thin-walled vascular channels. Most of the islet cell adenomata seem to fall into this general histologic category, showing some fairly narrow cords of cells but with many broader bands and clusters of cells. In other instances the exaggeration of the normal structure is in the opposite direction. Very long narrow cords of cells, only 1 or 2 cells thick, form more or less parallel, undulating and anastomosing bands separated from one another by delicate capillary channels. This "ribbon pattern," as Laidlaw⁴⁰ pointed out, is practically identical with that observed in hypertrophy of the islands of Langerhans in cases of diabetes as described by Weichselbaum and Stangl,⁶⁶ MacCallum⁴⁶ and Cecil.¹⁴ Finally, there is observed in a few islet cell adenomata the formation of small rosette-like clusters of columnar cells radiating from a center at which a minute lumen may be seen. Such structures, too, occasionally occur in normal islets. Laidlaw⁴⁰ referred to these as rosettes of cells formed around capillaries, but Isaji³⁴ interpreted this arrangement as evidence of the formation of short tubules. It is a matter of importance in relation to the genesis of these tumors that true ducts and ductules are often found well within the limits of the tumor mass and that they frequently show continuity with the islet cells of the tumor.^{12,22,23,25,32,40,44,51,68,73}

Isaji³⁴ suggested that islet cell adenomata be classified on the basis of histologic arrangement as "simple solid," "trabecular" (Laidlaw's "ribbon" type), and "partly tubular"; but deviations from the standard patterns render it difficult to apply this classification rigidly. Laidlaw⁴⁰ described 2 tumors showing the "ribbon" pattern and regarded this as a most unusual arrangement, stating that he was not aware of any previous description of it. On the other hand, Isaji³⁴ accepted no less than 9 previously reported adenomata as belonging to this category and stated that these "trabecular" tumors occurred with about the same frequency as the "simple solid" adenomata.

The individual cells composing the islet cell adenomata are also strikingly similar to those of normal islands, especially in the most highly differentiated tumors. In such instances they are of polyhedral, cuboidal, prismatic or columnar shape, depending upon their position in the sinuous cords and lobules. The nuclei occupy a position near the centers of the cells. In those tumors composed of wide bands and clusters, the centrally placed cells are mostly rounded or polyhedral but those which lie next to the vascular partitions are apt to be low or high columnar, forming a peripheral band around each lobule. The nuclei frequently lie toward the capillary poles of these cells. Thus, if there is disintegration of the central cells, the appearance of spaces apparently lined by columnar epithelium may suggest duct formation. In the adenomata of "ribbon" or "trabecular" type, the cells are columnar and lie in a direction transverse to the long axis of the ribbon with both poles of many cells in contact with capillaries. In this case, the nucleus lies near the middle of the cell. Such columnar cells may give the illusion of being abnormally large, but Laidlaw⁴⁰ found by actual measurement that they are no larger than many normal islet cells. Nevertheless, the tumor cells are frequently described as being considerably larger than normal.

The nuclei in general are much like those of normal insular cells. They are spherical or slightly ovoid, seldom elongated, varying in size from normal to about one-half again as large as normal. The chromatin content also varies so that the nuclei, though usually vesicular with clearly visible nucleoli, may in some instances appear almost pyknotic. Mitotic figures have been found in varying numbers in some adenomata^{22,40,51,58} but in most instances they are absent. The occurrence of binucleated cells and giant cells with central clusters of nuclei has been recorded by O'Leary and Womack,⁵¹ Kalbfleisch³⁷ and Friedman.²³

In tissue fixed in any of the ordinary fixing solutions and stained with hematoxylin and eosin or with eosin-methylene blue, the cytoplasm of the tumor cells is found to be definitely acidophilic in contrast to the basophilic cytoplasm of the acinar cells of the pancreas.^{32,60,64a} In fresh unfixed and unstained fragments of tissue immersed in Ringer's solution, individual cells can be seen to be packed with minute refractile cytoplasmic granules^{13,25,51,73} as are the cells of normal islets.^{6a,16,39,50} Careful histologic studies of these specific granules require special tissue fixation and special staining methods. Accordingly, such studies have been carried out chiefly in cases of hypoglycemia in which the pathologist, forewarned, was able to secure prompt fixation of the tissue in appropriate solutions.

The method of Lane,⁴¹ who in 1907 first distinguished between what he named alpha and beta cells, required fixation in 70% alcohol as well as in a chrome sublimate solution. In the former, the granules of the B (majority) cells were dissolved out and the granules of the A (minority) cells could be stained with neutral gentian. With chrome sublimate fixation, the granules of the B but not of the A cells were stained by neutral gentian. Since that time various staining methods have been devised by which the granules of alpha and beta cells are differentially stained in the same section when the tissue is fixed in aqueous solutions so that alcohol fixation is no longer necessary. Nevertheless, O'Leary and Womack⁵¹ have pointed out discrepancies in the results of some of these staining methods and recommended that comparisons which necessitated assigning types to islet cells be made by the original method of Lane. Different investigators have used various types of fixing solutions, including Zenker's stock solution, Zenker-acetic, Zenker-formol (Helly's), Bouin's and Altmann's fluids as well as Bensley's acetic osmic dichromate solution.⁵¹ Fixation in Zenker's, Helly's or Bouin's fluids gives satisfactory results. The special stains most frequently employed are the Mallory-Heidenhain azan stain, and the neutral dyes of Bensley^{6a} and Bowie.⁹ Laidlaw⁴⁰ found the neutral dyes "exasperatingly capricious" when applied to human material, but Bensley's acid fuchsin-methyl green^{6a} gave accurate and constant results. Modified fixing solutions and new staining methods have recently been described by Bayley⁵ and Gomori.^{24a}

By the application of one or other of these special staining methods, it has been shown that a varying proportion of the cells composing islet cell adenomata possess granules which stain like those of normal beta cells.^{11-13,23,25,32,40,51,60,64a,68,73} It is thought that the B cells of normal islets are the ones responsible for the elaboration of insulin and it is, therefore, worth noting that such cells have been demonstrated in symptomless adenomata^{60,64a} as well as in those with associated hypoglycemia. Studies of adenomata which produced no symptoms and were discovered as incidental findings at autopsy have gone not much farther than this because of the difficulty in demonstrating the specific granules in any but the freshest of autopsy material. In the case of adenomata causing hypoglycemia and excised surgically or obtained at an autopsy

expeditiously performed, the opportunities for histologic study are better and in some such instances cells containing granules like those of A cells have also been described as occurring in varying proportions with those of B type.^{12,25,32,40} Laidlaw⁴⁰ stated that the tumor cells stain exactly like those of normal islets, most of them containing granules of B type with here and there a cell containing granules of A type. However, as early as 1929, Robinson³² described certain cells in an islet tumor in which granules of both A and B type were present in the same cell. Prof. R. R. Bensley, whose opinion is quoted by several authors,^{13,25,60,62,73} and O'Leary and Womack⁵¹ drew attention to other points of difference between the tumor cells and normal cells of the islets of Langerhans. On the basis of meticulous studies of several different adenomata, Bensley,^{25,73} while admitting that the cells bore a considerable resemblance to those of normal islets, a few staining exactly as do normal beta cells, concluded that many of the tumor cells differed from the normal in several important cytologic details. He regarded these as abnormal beta cells. O'Leary and Womack⁵¹ concurred in this view and suggested that the severity of symptoms might be determined by the degree of similitude of the majority of the cells to the B cells of normal islets, as well as by other factors such as the intimacy of relation between the cells and vascular channels, the size of the tumor and the development of degenerative changes. Cells resembling the granule-free C cells of Bensley⁶ or the D cells of Bloom⁸ are lacking in islet cell adenomata.^{40,51}

Hydropic degeneration of the tumor cells such as might suggest excessive secretory activity has not been observed.^{40,51} In normal islets other forms of cellular degeneration are rare, but in islet cell adenomata pyknosis of nuclei with diffuse basophilic staining of the cytoplasm is frequently seen in small groups of cells.⁵¹ Moreover, in some of the reported tumors there were focal areas of necrosis occupied by cell debris mixed with red blood cells.^{13,25,51,73} O'Leary and Womack⁵¹ were unable to find convincing evidence that these manifestations of degeneration were entirely attributable to poor blood supply since they sometimes occurred in the neighborhood of apparently functioning vessels.

"Just as the tumors duplicate the structure of normal and hypertrophied islets, so they are subject to the same pathological vicissitudes such as fibrosis, hyaline degeneration and calcification" (Laidlaw⁴⁰). Fibrosis begins with an increase of the delicate fibrous framework surrounding the vascular channels and proceeds to the formation of broad bands of collagenous connective tissue which separate the constricted strands and clusters of tumor cells from the blood-vessels. These fibrous bands show a marked tendency to undergo hyalinization and, as elsewhere in the body, the hyaline material is apt to become calcified. Shields Warren^{64b} and O'Leary and Womack⁵¹ regard the hyaline material as being derived from the connective tissue and possibly from endothelial cells. Laidlaw,⁴⁰ on the contrary, is convinced that degenerating tumor cells also contribute to the formation of the hyaline masses. The extent to which these tumors may be replaced by fibrous, hyaline or calcified tissue has suggested the possibility of spontaneous cure of hypoglycemic symptoms caused by an islet cell adenoma, but no authentic instance of this has been recorded.

Possible Malignancy of Certain Islet Cell Adenomata. As has been mentioned already, certain circumscribed islet cell tumors have been described which lacked metastases and gave no other gross indication of malignancy but which possessed histologic features suggesting this possibility. The problem presented in such instances has recently been discussed by Frantz²² who collected from the literature the cases of this kind reported up to the end of 1939 and described several additional cases making a total of 21. The histologic findings upon which most emphasis has been placed as indicative of possible malignancy are incompleteness of encapsulation, and invasion of the capsule or of the adjacent pancreas or of blood-vessels by the tumor. Marked variation in size, shape or staining qualities of the tumor cells need not necessarily be an associated finding and mitotic figures may be totally lacking. Indeed, several authors, while making a diagnosis of carcinoma in such cases, have expressed doubt as to its correctness or have at least suggested that the tumor was of low-grade malignancy.^{22,25,32,48,51,54,62,73}

Clinical data support the view that these tumors, in spite of their histologic appearance, behave as benign neoplasms. Symptoms of hypoglycemia, evidently indicating the existence of the islet cell tumor, were present in these cases prior to operation or autopsy for periods almost always longer than 1 year up to 5,²⁵ 7,³² or 8 years.⁵⁴ Yet no metastases were found and surgical excision of the primary tumor in the pancreas was followed by the disappearance of hypoglycemic symptoms. No instance of recurrence of the tumor growth following operative removal has been reported, while survival for periods of 1 year up to 5 years or more without the recurrence of hypoglycemic symptoms has been recorded in 10 cases.²²

In the case reported in 1929 by Howland, Campbell, Maltby and Robinson,³² the patient suffered from symptoms of hypoglycemia for 7 years before they were relieved by surgical excision of a tumor diagnosed histologically at the time as a slow-growing carcinoma of the islets of Langerhans. No tumor metastases were found at operation. Dr. W. L. Robinson kindly informed the Reviewer in a personal communication in December, 1941, that this patient was still alive and well, more than 12 years after operation and 19 years after the onset of symptoms attributable to the presence of the tumor. Dr. Robinson stated that in view of this long period of survival and after reviewing the original histologic sections in the light of experience with tumors subsequently studied,¹² he is now of the opinion that the tumor in the first case was not truly malignant. Tempting as it is to do so, the same conclusion cannot yet be drawn with finality concerning all the remaining cases in this group. It is important that these patients should be followed and the ultimate findings recorded for the guidance of both clinician and pathologist.

Associated Changes in Endocrine and Other Organs. Hypertrophy of the islets of Langerhans has been described in a few cases in association with islet cell adenomata of the pancreas,^{23,34,37,44,45,61} but this does not occur with any regularity and in most instances the islets are histologically normal.^{51,60,64} There is no histological evidence of excessive secretory activity on the part of the islets and, indeed, direct evidence to the contrary is provided by the disappearance of symptoms of hypoglycemia after surgical excision of an islet cell adenoma.

Among associated lesions in other endocrine organs, various changes in the anterior lobe of the pituitary gland are the most frequent, though by no means common. Diffuse hyperplasia of eosinophil cells,⁴⁷ adenomatous hyperplasia of eosinophil and basophil cells,²³ basophil or chromophobe adenomata^{23,37,44,47,53,61} and marked invasion of the posterior lobe by basophils^{23,53} have been described in individual cases. Adenomata of the thyroid^{27,47} and parathyroids^{37,44} and enlargement of the thymus gland^{37,53,61,75} have also been observed as relatively rare associated lesions. In some instances, several of these lesions have been encountered in the same case together with islet cell adenoma, notably in the cases reported by Lloyd,⁴⁴ Rienhoff and Lewis,⁵³ Kalbfleisch³⁷ and Friedman.²³ The exact relation between these various changes in endocrine organs is not clear.

The liver is generally found to be essentially normal. Estimations of liver glycogen in several cases with hypoglycemia have shown considerable variations. Small to large amounts of glycogen have been demonstrated in a few instances,^{17,45,47,69,75} while in other cases glycogen was virtually absent from the liver.^{53,57,61}

In patients with a history of hypoglycemia various microscopic changes have been found in the brain and these have been variously interpreted.^{1,23,47,48,61} Perivascular petechial hemorrhages throughout all parts of the brain are common. Nerve cells in all layers of the cerebral cortex, in the basal nuclei, midbrain, pons, medulla and, to a lesser extent, in the cerebellum, are described as showing acute degenerative changes with swelling, chromatolysis and distortion of cell outline. Progression of these changes to complete disintegration of nerve cells with secondary glial proliferation has been described in some instances.^{47,48} Such widespread degenerative lesions have generally been regarded as significant, but Baker and Lufkin¹ believed that the acute degenerative changes observed in their cases had occurred post-mortem. The petechial hemorrhages have usually been interpreted as the result of convulsive seizures.

Islet Cell Carcinoma. Undeniably malignant islet cell tumors are rare. In only 6 reported cases has the hypoglycemic syndrome been observed in association with such tumors and cases of islet cell carcinoma without symptoms of hypoglycemia appear to be equally rare. However, in the absence of hypoglycemic symptoms, an islet cell carcinoma is less likely to be recognized as such. Peculiar tumors of the pancreas have occasionally been reported which might well have been unrecognized islet cell carcinomata, for example, the diffuse carcinoma of the pancreas of "rare type" with unusual metastases described by Willis.⁷⁰ Moreover, at least 1 functioning and 4 non-functioning islet cell carcinomata have been mentioned in passing by different authors without details of the cases being given.^{18,24,44} The 9 cases which have been reported in some detail are summarized in Table 1 and equivalent information is included regarding 3 cases merely mentioned by the Reviewer in a previous publication.¹⁸ The "adenoma malignum" of islet cell type described by Vecchi⁷³ is omitted since metastases were lacking and there was no other good evidence of malignancy. In addition to its occurrence in man, islet cell carcinoma of the pancreas has been discovered twice in dogs.^{10,59}

TABLE 1.—TWELVE CASES OF ISLET CELL CARCINOMA.

Authors.	Sex.	Age.	Hypoglycemic syndrome.	Total duration of illness (mos.).	Site of primary tumor.	Sites of tumor metastases.
Wilder, Allan, Power and Robertson ⁶⁹	M	40	Present	20	Tail of pancreas	Regional lymph nodes, liver, mesentery
Judd, Faust and Dixon ³⁶	F	18	Present	4½	Whole pancreas	Liver (no autopsy)
Bickel, Mozer and Junet ⁷	M	56	Present	20	Body and tail of pancreas	Liver, gall bladder, peritoneum, adrenals, pericardium, myocardium, pleura, lungs
Cragg, Power and Lindem ¹⁷	F	41	Present	8½	Whole pancreas	Abdominal lymph nodes, liver
Joachim and Banowitz ³³	F	31	Present	2	Terminal half of pancreas	Regional lymph nodes (no autopsy)
Ballinger ³	M	53	Present	9	Aberrant pancreatic tissue in liver	Abdom. and mediast. lymph nodes, spleen, adrenals, kidneys, mesentery, lung, myocardium, subcutan. nodule (rt. clavicle)
Zanetti ⁷⁴	M	56	Not mentioned	?	Whole pancreas	Regional lymph nodes, peritoneum, stomach, liver
Hamdi ¹³	M	52	Not mentioned	?	Tail of pancreas	Liver
Evangelisti ¹⁹	M	65	Not mentioned	?	Body and tail of pancreas	Liver, omentum
Duff ¹⁵	M	32	Absent	3	Whole pancreas	Reg. lymph nodes, liver, peritoneum, pericardium, thyroid, adrenals, renal glomeruli, vertebrae
Duff ¹⁵	M	60	Absent	7	Whole pancreas	Abdom. and mediast. lymph nodes, liver, kidney, myocardium, lung, subcutan. nodule (left clavicle)
Duff ¹⁵	M	45	Absent	5½	Whole pancreas	Abdom., mediast., cervical and axillary lymph nodes, stomach, liver, gall bladder, peritoneum, adrenal, pituitary, kidney, ureter, bladder, lungs, brain

In view of the small number of cases available for analysis, it can only be stated that the sex and age incidence of islet cell carcinoma of the pancreas does not appear to differ materially from that of other types of pancreatic carcinoma.¹⁸ These few cases show a ratio between males and females of 9 to 3, as compared with a ratio of only 4 to 3 among cases of islet cell adenoma (including those suspected of being malignant). It is perhaps worthy of note that the very young and the very old are not represented in this group as they are among the cases of islet cell adenoma.

The clinical signs and symptoms in 6 cases were predominantly those of hypoglycemia; the malignant neoplasm as such scarcely influenced the clinical picture. On the other hand, in at least 3 cases there was no clinical evidence of hypoglycemia and the clinical course did not differ from that observed in cases of carcinoma of the pancreas of other histologic types. Regardless of the character of the clinical picture, the duration of illness, from the onset of symptoms to death, was longer than 1 year in only 2 cases and in the majority it was much less than a year. This is in marked contrast to the long periods of illness prior to operation and the even longer periods of survival in good health following excision of circumscribed islet cell tumors in those cases in which the tumors were suspected of being malignant on histologic grounds.

The fact that the islet cell carcinomata in the 12 tabulated cases occupied either the tail, or the tail and the body, or the tail, body and head of the pancreas recalls the greater frequency of occurrence of islet cell adenomata in the tail of the pancreas, as compared with the body and in the body as compared with the head. The part of the pancreas occupied by the carcinoma is usually described as being somewhat enlarged and firm, rubbery or even stony hard. If the surface of the pancreas is not obscured by fusion with neighboring structures, it is found to be gray and fibrous in appearance with smoothly rounded contours interrupted in some cases by nodular projections of yellowish-gray tissue. The cut surface reveals replacement of the normal pancreatic lobules by broad areas of firm, gray, coarsely lobulated tissue, resembling fibrous tissue, which merges imperceptibly into the adjacent intact pancreas. In some instances such tissue may be seen, even at some distance from the main tumor mass, spreading out between the pancreatic lobules and blurring their outlines. In about one-half of the cases, distinctly yellow or reddish-yellow nodules, from a few millimeters to 1.5 cm. in diameter, are found embedded in the gray tumor tissue. Such masses may produce a nodular irregularity of the external surface of the pancreas. While the tumor mass may, in some instances, be fairly sharply demarcated from the neighboring pancreatic tissue, gross encapsulation of the mass has never been described. Metastatic tumor nodules may be circumscribed or infiltrating; the tissue is firm but, like that of the primary tumor, varies in color from gray to reddish-yellow.

The resemblance between the histologic structure of these tumors and that of normal islets of Langerhans has been repeatedly commented upon. This similarity is most striking in small outlying nests of cells which may be extraordinarily difficult to distinguish from normal islets.¹⁷ Even in the midst of the tumor mass, rounded structures may be encountered that look like giant islands occurring in masses, some of which are large enough to be grossly visible.²¹ Apart from such circum-

scribed structures, however, the tumor takes a diffuse infiltrating form with the tumor cells arranged in rounded clusters or irregular cords separated either by delicate strands of connective tissue carrying numerous capillaries or by broad dense fibrous bands. The clusters and cords of cells are solid and there is no tendency toward the formation of glandular structures or ducts but progressive degeneration and necrosis may lead to the development of cystlike spaces.⁷

The smaller tumor cells resemble normal islet cells very closely, possessing a vesicular nucleus with a distinct nucleolus and eosinophilic granular cytoplasm. In a few cases, the cells were uniformly of this small type,^{17,19,28} but considerable variation in size and shape of the cells is the rule. Cells somewhat larger than normal frequently contain large hyperchromatic nuclei and scanty cytoplasm. Multinucleated giant cells have been described in 2 cases.^{2,7} Mitotic figures, some of them atypical, are generally present, though in varying numbers. The histologic structure of the metastases is similar to that of the primary tumor, but in several instances there have been observed histologic differences of such a character as to suggest more rapid growth in the metastases than in the primary pancreatic tumor.

The demonstration of specific cytoplasmic granules in the tumor cells has been attempted in only 1 of the tabulated cases and in 1 other. Joachim and Banowitz³⁵ were able to find a few granules which stained like those of B cells, but Gomori^{24b} stated that the tumor cells in his case contained no identifiable granules.

From all of the available information, it would appear that islet cell carcinoma of the pancreas is a rather rapidly growing tumor which spreads quickly from the pancreas into neighboring structures and metastasizes widely by way of both lymphatic and blood channels. The tendency of the tumor to spread rapidly beyond the limits of the pancreas might be regarded as a property inherent in this particular tumor were it not known that the same tendency is shared in equally marked degree by pancreatic carcinomata of other histologic types when they are located in the body or tail of the pancreas. This fact has been pointed out by the Reviewer in a previous publication and the phenomenon explained on purely anatomic grounds.¹⁸

Genesis of Islet Cell Tumors. The studies of Bensley,⁶ Grauer²⁶ and others on the embryology and regeneration of the pancreas have firmly established the view, now universally accepted, that the epithelial cells of the islets of Langerhans are derived by differentiation from the epithelium of pancreatic ductules. In the embryo, the pancreas develops from hollow epithelial buds which grow out from the duodenum as branching pancreatic ducts. At intervals along these proliferating ducts, differentiation of the epithelium occurs in two distinct directions giving rise either to acinar cells or to islet cells. This ability of the duct epithelium not only to form new ducts but to differentiate into acinar or islet epithelium is certainly carried beyond the period of embryonic development and apparently persists throughout life. In adult animals, ligation of the pancreatic duct is followed in a short time by degeneration of the pancreatic acini and by a more gradual disappearance of the islets of Langerhans. So long as the duct remains occluded, attempts at the regeneration of pancreatic acini are constantly frustrated by degeneration of acinar cells as quickly as they are

formed.⁶ However, the reestablishment of duct drainage is followed by rapid and successful regeneration of acini from the duct epithelium.²⁶ On the other hand, even if occlusion of the pancreatic duct is permanent, the islets of Langerhans are replaced, almost as rapidly as they are destroyed, by new islets originating by differentiation from epithelial cells of the pancreatic ductules.⁶ Once differentiated out from the duct epithelium, the islet cells are capable of independent proliferation.

On the basis of this knowledge, it has been suggested by O'Leary and Womack⁵¹ and Laidlaw⁴⁰ that islet cell tumors represent a response of pancreatic duct epithelium to a stimulus which calls into action its islet-forming potentiality and, to a lesser extent, its ability to build ducts, while its power to form pancreatic acini remains virtually in abeyance. This suggestion is supported by the frequent presence in islet cell adenomata of pancreatic ducts and ductules^{12,22,23,25,32,40,41,51,68,73} in such numbers that at least some of them must be regarded as newly formed.⁴⁰ Still stronger support comes from the observation of direct continuity between the epithelium of these ductules and the islet cells of the tumor.^{23,25,40,51,73} O'Leary and Womack⁵¹ have even identified single islet cells interspersed among the cells lining the ducts. Moreover, they repeatedly noted the presence of mitotic figures in islet cells containing specific granules, indicating the ability of these cells to carry on independent proliferation once they have differentiated out from the duct epithelium. Although these observations have been made exclusively in islet cell adenomata, it seems justifiable to apply the obvious conclusions to the genesis of malignant islet cell tumors as well.

The ability of the multipotent pancreatic duct epithelium to give origin to islet cell tumors in the pancreas must surely be duplicated in aberrant pancreatic tissue which is usually composed of pancreatic ducts and acini, often with well-formed islets of Langerhans. Pancreatic tumors of other kinds certainly may occur, as exemplified by the adenoma of duct or acinar type discovered by Schmidt⁵⁵ in a nodule of accessory pancreatic tissue in the wall of the jejunum. However, so far as the Reviewer is aware, there have been only two reports of the occurrence of islet cell tumors in aberrant pancreatic tissue. Vecchi,⁶³ some years ago, described a large islet cell adenoma which had developed in accessory pancreatic tissue located near the tail of the pancreas. The second instance is that recently reported by Ballinger² in which hypoglycemia was associated with an islet cell carcinoma originating in aberrant pancreatic tissue in the liver (see Table 1). Faust and Mudgett²⁰ have recently collected from the literature 370 cases of aberrant pancreas. Their analysis of the distribution of the aberrant tissue shows that it was located most frequently in the wall of the duodenum (30%), stomach (26%), jejunum (18%) and ileum (13%); other rarer sites included the gall bladder, spleen, mesentery and omentum. It seems obvious that islet cell tumors may be expected to occur rarely in one or other of these situations.

G. LYMAN DUFF, M.D.

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PREVENTIVE MEDICINE AND EPIDEMIOLOGY.

UNDER THE CHARGE OF

JOHN E. GORDON, M.D.

PROFESSOR OF PREVENTIVE MEDICINE AND EPIDEMIOLOGY, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS.

FAMILIAL AGGREGATION IN POLIOMYELITIS.

THERE are epidemiologic indications that the development of paralytic poliomyelitis in the few of the many who come in contact with the virus may be determined not so much by parasitic or environmental factors of exposure, but rather by autareeologic susceptibility of the host.^{1b,c} In a smaller proportion of cases, certain temporary or changing influences^{1h, i, 4, 6, 8, 9, 22} in the individual, operative at the time of development of the disease, clearly affect the outcome of exposure to the virus. But a number of selectivities in the occurrence of the frank disease among those exposed indicate that susceptibility to paralysis is even more often inherent.^{1c-f}

It should be clearly in mind that susceptibility to paralysis must await exposure to the virus for its expression. Otherwise, confusion arises when an attempt is made to reconcile the distribution of the frank disease with the idea of susceptibility as an important determinant of paralysis. Thus, an eminent epidemiologist once rejected the whole idea of individual susceptibility to paralysis on the grounds that such a susceptibility could not by any stretch of the imagination occur radially (in the manner of spread of epidemics of the disease).

It is recognized, of course, that the development of poliomyelitis is immediately dependent on exposure to the virus and that many of the features of the distribution of the disease tend rather to reflect the distribution of the virus. For example, it is now clear that the age distribution of the disease is determined by the time (or average age) of exposure to the virus and may be limited by immunity from previous exposure, rather than by variations in susceptibility with age *per se*.^{1a, 3a-c, 10, 26}

What is determined by inherent or natural immunity (autareesis) is the limited and selective occurrence of paralytic poliomyelitis in those exposed to its virus. It is this aspect of the disease that takes away from the presenting epidemiologic picture the readily apparent criterion usually sought to establish contagion—the occurrence of the disease among those directly associated with the sick—and which accounts for the ease with which the whole subject of transmission can be reopened by the advancement of any new hypothesis, based on even fragmentary observations on some feature of the distribution of the more apparent clinical disease when not viewed in the light of the less apparent but much more widespread dissemination of the virus.

Because of the indirect nature of much of the evidence for it, the epidemiologic concept of widespread dissemination of virus originating in the now classic observations of Caverly and Wickman has been subjected to many checks and challenges. The basic evidence lies in the unbroken gradation from frank paralytic cases of the disease through milder and non-paralytic forms to suspected abortive infections; in the

time and space relationships between clinically recognizable cases which imply intervening milder infections or healthy carriers; and in the occurrence of extensive immunity in the general population as shown by virus neutralization tests.^{3a-c} The concept of widespread virus is at the present time being rapidly substantiated by new procedures for the detection of virus, not only in recognizable cases but in suspected illnesses and healthy individuals as well.^{15,20} Only when the distribution of the frank disease is examined in the light of widespread virus does it become possible to discern the selectivities which indicate inherent or familial susceptibility to paralysis as the factor which determines this complication in the few of the many exposed. The pattern of paralytic disease occurrence is formed by interceptions of the pattern of susceptibility to paralysis by that of virus distribution.

Doubtless much of the confusion which has entered into the formulation of a generally acceptable concept of the natural history of poliomyelitis has arisen from the difficulties in establishing either of the two variables which determine the pattern of disease distribution, when this resultant pattern has been the one directly presenting itself for study. Now that one of these determining patterns can be more or less held fixed as a variable, the other can be brought nearer the surface for examination.

In this paper are reviewed several sets of observations,¹¹ all of which, under the concept outlined, are consistent with hereditary susceptibility as a factor which determines the occurrence of paralysis in a selected few of the many exposed to the virus. The data do not represent a systematic tabulation of the different categories of cases as to frequency of occurrence in a given population or series of cases. They have been accumulated over a period of years in the course of various studies in numerous localities, and hence no comparison can be made with any calculated expectancy. For these reasons, no one of the group of instances can be considered in itself proof of the operation of hereditary factors in the distribution of paralytic poliomyelitis. But from the rareness with which some of the instances would be expected to occur by chance in the distribution of a relatively uncommon disease, the observed frequencies are suggestive of hereditary factors in the distribution of paralytic poliomyelitis. Furthermore, the different categories of instances occur in general in the proportion to each other which would be expected in a disease influenced by heredity. Although the nature of the data available precludes exact comparisons, there are certain indications that the frequency of the different categories of instances is of the same order as is observed in corresponding instances of certain other diseases in which hereditary influences operate.^{10,13,14} Family composition itself, of course, is one factor in determining the relative proportions of some of these instances and would be a more decided determining factor, for example, between one disease preponderantly of childhood and another preponderantly of adult life. Because of the more or less general agreement between the frequency of these instances in poliomyelitis and in diabetes (a non-infectious disease occurring with a very different age distribution), to be shown later, we are inclined to the view that the relative frequencies of the different instances recorded here are indicative of hereditary factors influencing the distribution of poliomyelitis.

Multiple Cases in Families. The first of these observations is a re-interpretation of certain data relating to the frequency of multiple cases of poliomyelitis in families. One of the commonplace arguments against the widespread and easy transmission of the virus from person to person has been the infrequency of multiple cases in families, which has been commonly interpreted as evidence that the virus of poliomyelitis is less communicable than those of other common infectious diseases which tend to spread through families. This idea was emphasized in an early study by Hill¹¹ in Minnesota, where he "compared the relative transmissibility of infantile paralysis with that of scarlet fever, diphtheria and typhoid fever in the same territory." Of persons known to have been exposed to diphtheria, scarlet fever and infantile paralysis, the percentages contracting the disease were: scarlet fever, 22%; diphtheria, 17%; infantile paralysis, 6%. Taking the instances of these diseases where 1 case existed in a family, other cases occurring in the family were as follows: scarlet fever, 40%; typhoid fever, 30%; diphtheria, 29%; infantile paralysis, 17%. From these observations, Hill concluded that poliomyelitis is less transmissible than scarlet fever, typhoid fever, or diphtheria. From these and similar findings, it was concluded by certain students, many years ago, that "such instances are difficult to explain by any theory of personal contact, direct or indirect."¹⁸

Lavinder, Freeman and Frost,¹⁷ from detailed comparisons of secondary attack rates in poliomyelitis, scarlet fever and diphtheria, concluded that secondary attack rates indicate quite striking differences in the liability of persons exposed in the family with a case of the disease to contract it. In poliomyelitis, only 1 person in 100 exposed in the family with a case developed the disease, while in scarlet fever the proportion was 1 in 10, and in diphtheria 1 in 16 in those so exposed.

On the other hand, the striking manner in which poliomyelitis sometimes runs through several members of a family under the same conditions of exposure where only 1 member is usually attacked has long suggested a family tendency.²⁵ Marie¹⁹ and also Charcot, of the early French writers, laid great stress on the hereditary nature of the disease, pointing to its known occurrence in several members of the same family as evidence of a hereditary influence. Stephens,²³ reporting an outbreak in Victoria, Australia, in 1908, makes the statement that there is a family predisposition to the disease in some instances.

In 1925, Aycock and Eaton,² in the course of a study of the interval between multiple cases of poliomyelitis in families, made some calculations (unpublished) on the probability of the occurrence of additional cases in a family into which the disease was introduced, and found that the attack rates in remaining members increased with the number of cases which had occurred. Because of the nature of the data and the methods of calculation, no conclusion could be drawn, but a family tendency was suggested.

Of these two contrasting points of view of the contagiousness of the virus of poliomyelitis, the latter seems preferable, since the observation made by Hill to the effect that poliomyelitis is less contagious than diphtheria and scarlet fever, and those by Lavinder, Freeman and Frost, generally interpreted in the same way, do not include adjustment for differences which would be expected in familial aggregation in relatively

rare and relatively common diseases in the general population. Now, if population saturation in poliomyelitis is equal to that of measles and diphtheria, for example, then poliomyelitis virus infection (not clinical disease) must be as contagious as those of measles and diphtheria, and there is no reason for supposing that any special condition of contagion would cause the spread of the virus of poliomyelitis, upon introduction into a family, to depart markedly from that of measles in a family. As is well known, measles tends to run through families, and as indicated by the weight of evidence in general and recently verified by virus detection studies such as that of Langmuir and McClure,¹⁶ the same holds true of poliomyelitis virus. Since measles is always clinical, the observance of cases in non-immunized members of families is a true measure of virus spread. But since poliomyelitis virus infection is silent in the vast majority, the same silence would be expected in families. Stated in another way, if the occurrence of secondary cases of measles in a family can be considered as reflecting the contagiousness of this virus in general, it would be expected—bearing in mind the relative infrequency of clinical poliomyelitis—that the occurrence of secondary cases of poliomyelitis in families, reflecting only in a small degree the contagiousness of this virus, should be correspondingly less. Since measles uniformly occurs in clinical form and clinical poliomyelitis occurs in less than 1 % of those exposed to its virus, it would be expected that the tendency to secondary cases of poliomyelitis in families would be of the order of 1 % of that observed in measles. Thus, the finding of a secondary attack rate in poliomyelitis, as in the studies of Hill and of Lavinder, Freeman and Frost, as high as one-fifth that of measles (Chapin⁷) is in reality indicative of a relatively high tendency to familial concentration of clinical poliomyelitis.

Recurrence in Siblings. Because of the relatively low incidence of poliomyelitis—the infrequency of outbreaks in an average community—recurrences in the same family would on the laws of chance be exceptional. During the course of observations covering a period of years, instances of poliomyelitis have been encountered in a brother or sister of some patient seen in previous years, or where some older brother or sister of the patient had residual paralysis from an earlier attack. Twenty-two families where dates and ages are known have been studied in detail.¹⁶ Chronic carriage of the virus on the part of the earlier case, or some household circumstance might be considered as the epidemiologic factor in the recurrence of the disease in the same immediate family. However, it was found that many of the later cases were not yet born when the earlier case occurred, and in several instances the older member of the family was no longer in the home when the later case occurred. Moreover, a number of these cases developed after the individuals had left home, or the families had moved to new localities or even to other countries in the interim between cases. There is one such instance in a family in which both the parents died while the children were infants. The two children were adopted in different localities and never saw each other again, yet each developed the disease at different places years after they had separated.

Due to the wide range of variation in the occurrence of the disease within the period and between the localities represented by these instances of recurrence, any calculated expectancy for statistical com-

parison with these observations would probably come no nearer answering the question than the impressiveness of the observation in view of the uncommonness of the disease in a given location.

Recurrence in Parent and Child. Another circumstance of familial recurrence of poliomyelitis to be considered in the present connection is the appearance of the disease in a child whose parent also had the disease in childhood. Such instances are more suggestive of a hereditary factor than recurrence in siblings, first because they include successive generations; second, because environmental or household influences which might enter into recurrence in siblings can be more definitely excluded; and, third, because the low incidence of the disease would render unlikely the occurrence on the laws of chance of any number of such instances.

Again, no useful comparison can be made with any calculated expectancy, but the number of instances of this type of recurrence appearing in the records of poliomyelitis in Vermont and Massachusetts (with some additions from studies made elsewhere by the author) are regarded as suggestive, when compared with the number of instances of the disease occurring at the same time in a parent and one or more children.

There are in our data 11 instances of simultaneous poliomyelitis in parent and child, which represent a fairly complete reporting of such cases actually occurring in the series from which they were taken, for the simple reason that the recognition of one case practically insured finding the other. On the other hand, the 38 instances of the occurrence of the disease in the offspring of individuals who had had it in childhood doubtless represent only partially the instances which actually exist in the series. These instances were not sought for systematically, and it was only in the course of other investigations that many times they came to light through finding a parent with a limp characteristic of poliomyelitis in whom such a diagnosis had never been made. It is felt that these instances of poliomyelitis in parent and child actually are of more frequent occurrence than is represented by the number we have on record.

Occurrence in Other Relatives. If recurrences of poliomyelitis in siblings and in parents and children are indicative of a familial tendency, recurrences in other relatives in both lineal and collateral lines should also be found. A study in Massachusetts and Vermont of 586 cases of poliomyelitis investigated serially with varying degrees of thoroughness revealed that 26.8% of them had one or more relatives with the disease other than members of their own household. In Massachusetts, 17.7% of the serial cases investigated gave a history of the disease in relatives, in Vermont 51.5%. In 133 family lines in Massachusetts with more than 1 case, the average occurrence was 2.8 cases per family; while in the 89 Vermont family lines with more than 1 case, the average was 3.2 cases per family. Several factors seemed to enter into the higher figure obtained in Vermont. First, many families still living in the old home with members of older generations were able in general to furnish more complete genealogies and had a more intimate acquaintance with their relatives and a better knowledge of their diseases than had residents of cities who were interviewed and who were out of touch with their relatives. Third, in certain local rural outbreaks, a large proportion of cases were observed in closely related individuals in the com-

munity. In one instance especially, doubtless due to the fact that the place had previously been inaccessible to transportation facilities for a good part of the year, a large proportion of the cases of the disease over a period of years occurred in a group of relatives in whom intermarriage was common. In some of these families, subsequent follow-up has revealed as many as 20 cases in the blood relatives of a patient.

In the course of this study in Massachusetts and Vermont, 100 individuals who had not had poliomyelitis themselves, nor had it occurred in their siblings, were chosen at random as a control. Only 5% of this group could cite single cases among their relatives.

Since New England is an area of comparatively high poliomyelitis prevalence, the familial occurrence of the disease in a southern state, where the reported prevalence is low, has been studied with similar results.^{1d}

Twins. Data concerning the occurrence of disease in twins have many times been used in studies of inheritance. Much can be learned from a comparative analysis of the incidence of a disease in similar and dissimilar twins, for if a condition is inherited, its incidence in both similar twins should far exceed its incidence in dissimilar twins. In Joslin's¹⁴ series of patients with diabetes (about 17,000), 48 pairs of twins suitable for analysis were found. Of these twins, 19 were similar in type, 29 dissimilar. In 12 of the 19 sets of similar twins, both were diabetic (63%), whereas in only 2 (7%) of the 29 pairs of dissimilar twins did both twins have the disease.

Our poliomyelitis data include 9 sets of twins, of which 4 sets are known not to be identical, where 1 developed paralytic poliomyelitis; 1 set (identical) where 1 developed paralytic and the other non-paralytic poliomyelitis; 1 set (not identical) where both developed paralytic poliomyelitis; 1 set (girls) who both had non-paralytic poliomyelitis; and 1 set (identical) who both developed paralytic poliomyelitis. In the 4 instances where both twins developed the disease, it occurred at the same time.

Double First Cousins. In the study of poliomyelitis in the relatives of 586 patients (with incidental additions from time to time as family histories have become available), exact relationships have been charted. On these charts there are 97 instances where 2 or more first cousins have had the disease, and 3 instances of double first cousins. In 1 of these, 2 brothers who had a first cousin with poliomyelitis married 2 sisters who had an aunt, a first cousin (daughter of the aunt), and 6 other blood relatives with poliomyelitis. Two children of 1 of these marriages had poliomyelitis in 1916, and 1 child of the other marriage, living in the same locality but not born until 1919, had poliomyelitis in 1921.

There are two additional instances of double first cousins where 1 had poliomyelitis and the disease occurred in the children of the other; and 2 instances where the disease is known in the grandchildren and great-grandchildren of double first cousins. In all of these instances, the disease is known in 1 or more other blood relatives.

Also included in this category is an instance where a son by a prior marriage and his father, with 1 other case in a relative, married 2 sisters in whose relatives 9 cases were traced. A child of the son and a grandson of the father by the second marriage developed poliomyelitis in the same city, 1 in 1916 and 1 in 1930.

Husband and Wife. From the fact that poliomyelitis is preponderantly a disease of younger years, it would be expected that more than 1 case in a family or household at adult age, as for example in husband and wife, would be exceptional. However, a number of instances do appear in our data in which the disease has occurred at adult age in 2 members of a family. The familial significance of these multiple adult cases lies in the fact that they are blood relatives—2 cases in adult siblings, and 1 particularly illustrative instance where 3 cases occurred at the same time—in a child, his father and an adult sister of the father; the wife in the household escaping.**

TABLE 1.—OCCURRENCE OF POLIOMYELITIS, DIABETES AND LEPROSY IN RELATIVES OF PATIENTS.¹

	Poliomyelitis.	Diabetes.	Leprosy.
Consecutive cases studied	586+*	523	100
Controls	100	153	
Patients with cases:			
In siblings	109	100	28
In parents	48	86	19
In other relatives	294	110	12
Total patients with cases in all relatives†	314	296	59
Total controls with cases in all relatives	5	26	
Instances in twins:			
One or both	9	48‡	
Both	3	14	
Identical twins:			
One or both	19	
Both	12	
Non-identical twins:			
One or both	29	
Both	1	2	
Instances in husband and wife	1	22§	5¶
In related husband and wife	1	1§	Yes¶

* Because of a number of later additions and overlapping due to more extended studies of some of the original cases, the exact number of cases cannot be stated.

† Patients are counted more than once if cases occurred in more than one category of relatives.

‡ From records of about 17,000 cases.

§ From records of about 1000 cases. (We are indebted to Dr. Priscilla White for these figures.) No special attempt was made to ascertain relationships between husbands and wives with diabetes.

¶ In the study by Hopkins and Denney¹² it is not stated whether conjugal cases are blood relatives, nor is it clear that the development of the disease was "conjugal" (marriage between patients already having leprosy are known); but in other studies (Rogers and Muir¹³), conjugal leprosy is exceptional. In the few instances of conjugal leprosy investigated by the author of the present paper, the conjugal mates have been blood relatives.

There are far more families where the 2 adult members are husband and wife (most often unrelated) than where the adults are blood relatives. In view of this circumstance, the striking rarity of conjugal

** Of interest in this connection, we find in the series of instances of poliomyelitis in parent and child 11 families with 20 cases in the relatives of the parent who had the disease, and only 4 families with 11 cases in the family of the parent who did not have the disease. In 3 families, there were other cases in the family of the parent who had the disease, as well as in the family of the one who did not have the disease; but in some there were interrelationships.

poliomyelitis (a phenomenon well known in leprosy) is in itself strongly suggestive of familial predilection. Moreover, in the 1 instance of simultaneous occurrence of the disease in husband and wife (in our records), which is discussed in the section on rural outbreaks, they were blood relatives.

Comparison With Other Diseases. As previously stated, the frequency with which the different categories of familial aggregation in poliomyelitis appear in this series is of the same general order as that observed for corresponding instances of other diseases in which hereditary influences operate. Available for comparison are the extensive studies of Joslin and his coworkers¹⁴ on diabetes and similar studies on the familial occurrence of leprosy by Hopkins and Denney.¹³ Corresponding figures for the three diseases are not always available and, due to differences in the methods of collection and analysis of data in the different series as well as certain discrepancies in the tabulations concerning poliomyelitis, exact comparisons are not always possible. Nevertheless, the relative frequency of the various categories of familial aggregation in three diseases, so widely different from an epidemiologic point of view, may be seen from the figures which have been assembled in Table 1 to be roughly comparable.

Other Circumstances Suggestive of Familial Predilection. Other observations, which do not lend themselves to any statistical analysis but which are equally impressive to the investigator in the present connection, are the finding of blood relationships between cases in localized outbreaks and cases which have been encountered consecutively in the course of various studies.

Successive Cases. About 10 years ago, while on a few days' visit to my home town in Georgia, a local physician asked me to see a child he "thought" had poliomyelitis, although he had never encountered a case in his practice in the town. The child had paralysis of the muscles of 1 leg and the diagnosis was verified. The mother of the patient, whom I had known since childhood, had always been lame with what I supposed was "white swelling." The father was also lame as a result of an injury. At the time, it seemed only oddly coincident that all 3 members of 1 family should be lame in the right leg—1 from tuberculosis of the hip, 1 from poliomyelitis, and 1 from an injury.

A few years later, when I became interested in the familial incidence of poliomyelitis, it occurred to me that the mother might actually have had poliomyelitis. On a subsequent visit, I was able to make a positive diagnosis by examination, and obtain the story that, in 1889, when Mrs. P. was about 5 years old, she had an illness which the doctor called typhoid fever, with the explanation that after a few days the fever settled in the leg and withered it.

Another of the few cases in this small town, where poliomyelitis has been rare, occurred the same year. In my childhood, there had been a colored boy who went about the streets in a goatcart, with atrophied, contracted and deformed extremities—poliomyelitis undoubtedly to me now. I located his father, Uncle Dad Martin, still living and over 85, he thought. He could give but meager information, but after some difficulty in establishing dates the story pieced together was that the boy had been well until he was about 5 years of age, in 1889. He was suddenly seized and, as the old man expressed it, "He jes got stiff, and

den he got limber, and nevah did walk no mo'," not too inaccurate a description of poliomyelitis obtained 50 years later, of rigidity of the spine, then flaccid paralysis and permanent disability.

In 1935, in Asheville, N. C., for a day seeing an acute case of poliomyelitis with members of the city health department: a sister of the patient came into the room with a gait typical of poliomyelitis, although the only diagnosis which had ever been made was that, as a small child, she had slipped on a rug and had been lame ever since. The family came from an adjacent rural county. Six months later, when passing through Asheville again, I encountered on the street a young man who was obviously an old poliomyelitic. The diagnosis was verified by examination. His name was the same as the patients of 6 months before, he had come from the same rural section, and was a relative.

In Raleigh, N. C., during an outbreak of poliomyelitis, two physicians in charge of a children's institution, in the course of a discussion of precautionary measures, both happened to mention that poliomyelitis

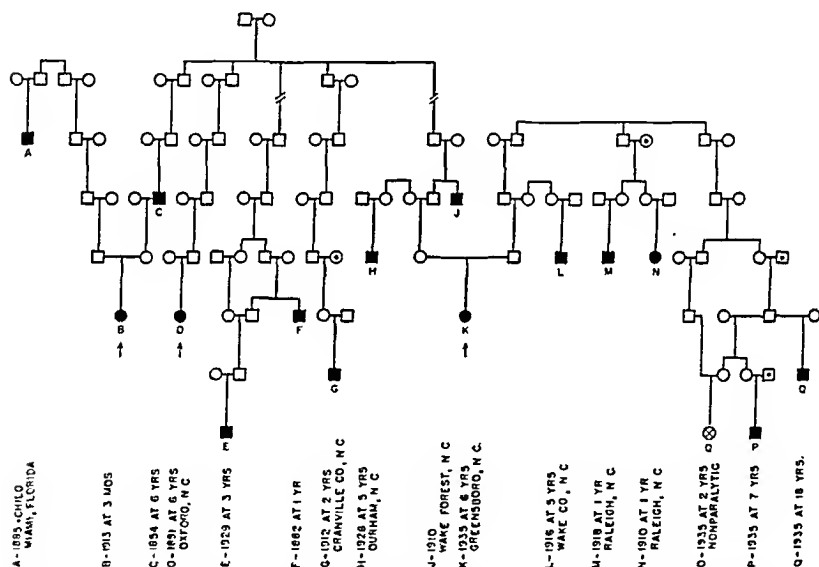


CHART 1.—Poliomyelitis. Three cases indicated by arrows were encountered consecutively. Their relationships to each other and to other cases as revealed by subsequent investigation are indicated. Some of the cases occurring in earlier years were verified by examination, others are included as cases of poliomyelitis because of histories from which a diagnosis could be made with at least reasonable certainty.

had occurred in their families, 1 in a daughter and the other in a sister. Their first response to the suggestion that they were related was that there was no kinship, but soon it developed that the mother of the second patient was related to the first patient.

The next day in Greensboro, N. C., seeing an acute case, I learned that the child's mother came from the same community as the two physicians I had met in Raleigh and was related to their families. Upon further investigation, 13 other cases of the disease were found among their relatives. These relationships are shown in Chart 1.

Isolated Rural Outbreaks. In the epoch preceeding the era of bacteriologic causation in disease, the prevailing view of leprosy, originating in studies of familial aggregation by Danielssen and Boeck in 1848, in an isolated and sparse focus of the disease in Norway, was that the disease was hereditary. The discovery of the Hansen bacillus in 1874 "threw a flood of light on the etiology of leprosy and revolutionized our entire conception of its epidemiology by displacing the then dominant and paralyzing hereditary theory of its origin by the now generally accepted and more hopeful infective one" (Rogers and Muir²¹).

These divergent concepts—heredity and contagion—derived at different periods, not so much from conflicting observations as from resisting inferences evolved from the same kind of observations, were formed long in advance of precise knowledge of the fields into which they led. Turning back to the data from which these earlier concepts evolved—each doubtless influenced at the time by the ascendancy of the field concerned—discrepancies in each and validities in both become apparent. The approval of either necessitates the rejection of valid evidence for the opposed theory as well as the acceptance of assumptions of doubtful worth in the theory favored. When the validities in the two conflicting hypotheses are reexamined in the light of advances in knowledge, they prove adjustable into a third and inclusive concept involving both contagion and hereditary susceptibility.^{10, 5, 12}

Similarly, in the epoch before the infection and its mode of spread became the central idea in its epidemiology, numerous studies of familial aggregation in poliomyelitis were interpreted as indicating an hereditary influence.^{19, 23, 27}

As Hirsch¹² pointed out in a discussion of hereditary predisposition in leprosy, "The best ground on which to try this question is obviously afforded by the small, closely circumscribed, and therefore easily surveyed leprosy spots, with a fixed population subject to no change, where the state of health in the several families may be learned with the least possible trouble and followed with certainty through a long series of generations." A number of rural outbreaks of poliomyelitis, in which the conditions conform to those prescribed by Hirsch as best suited to the study of familial predisposition, have been investigated.

Taylor²⁵ reported an outbreak of 7 cases of poliomyelitis in Cherryfield, Maine, in 1896: the second case was a brother of the first, and the third case was a cousin of the first and second cases.

Wickman²⁷ observed 54 cases during an extensive outbreak in Stockholm in 1899: "In several families 2 or 3 cases were observed among cousins, brothers and sisters."

Blackhall, reporting 6 cases in Queanbergen, New South Wales, in 1903-1904, observed that 2 cases were sisters and 2 were cousins.

In an isolated rural outbreak observed by the author in Coneord, Vermont, in September and October, 1922, a non-epidemic year, there were upwards of a dozen mild illnesses suspected as being abortive poliomyelitis, and 5 paralytic cases, all related, as shown in Chart 2.

A rural outbreak in Newbury, Vermont, in 1923, reveals a similar relationship between all paralytic cases. No circumstance in common could be established except residence in the same locality (but not on adjacent farms) and blood relationship between cases.

It was in this outbreak that the 1 instance of conjugal poliomyelitis (already discussed) occurred. For a number of years this circumstance was held as contrary to the idea of familial susceptibility, until kinship

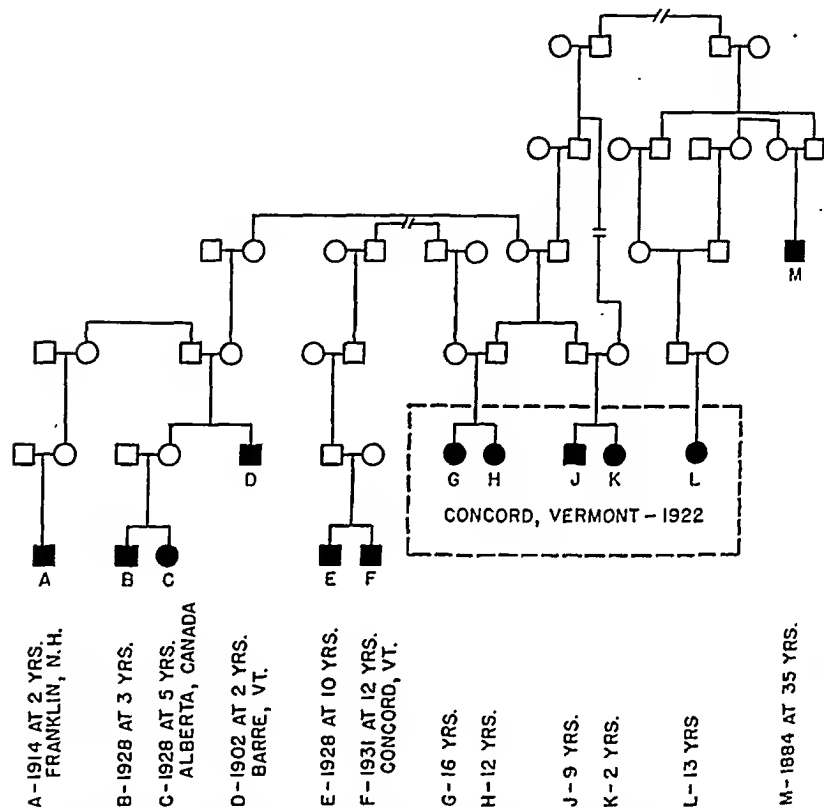


CHART 2.—Relationship between 5 cases of paralytic poliomyelitis occurring in an isolated rural outbreak of the disease and relationships to other cases at other times and in other localities.

between husband and wife came to light through tracing relationship of a later case in another part of the state to both of them (Chart 3).

An isolated rural outbreak in New York State in 1940, reported by Langmuir,¹⁶ is of particular interest in the present connection because of the fact that through virus detection studies carried out by McClure, the pattern of virus distribution in the outbreak was actually determined.

Following this outbreak, the virus of poliomyelitis was detected in a number of members of each of 4 families, usually the majority, by inoculation of fecal specimens into monkeys. In 3 of the families, paralytic cases occurred and in all 4 families involved there were non-paralytic or milder suspected abortive illnesses at the same time; while some of the members of each family remained well. The virus was detected not only in paralytic, non-paralytic and suspected abortive cases, but in healthy members of the families as well.

As revealed by a subsequent investigation with Drs. Langmuir,

McClure and Korns, relationship was established between 2 of the families in which 4 of the paralytic cases occurred, and probable relationship between these and the fifth paralytic case. All these cases carried the same family name, which probably traced back to 2 brothers who originally settled in the community but whose family lines have remained apart.

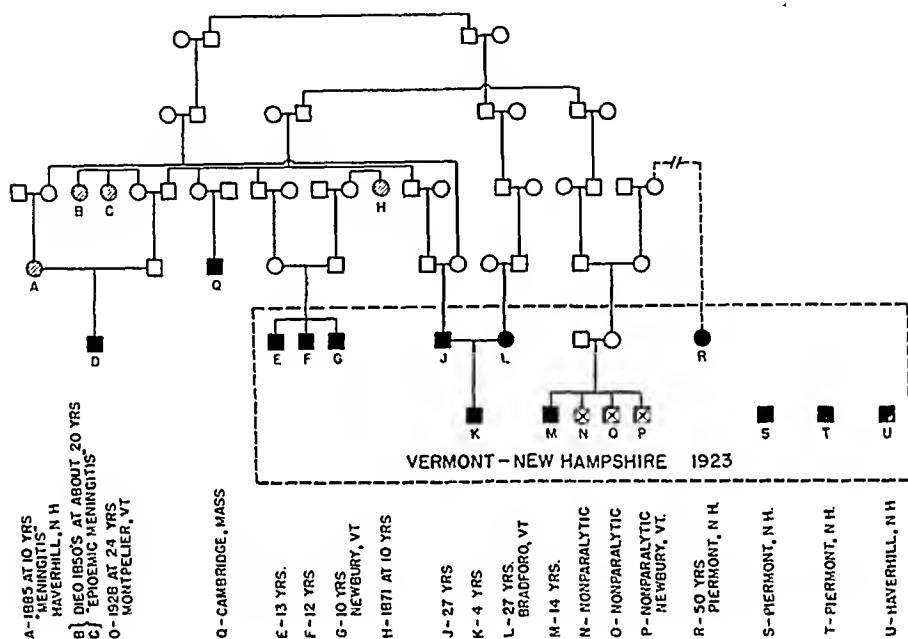


CHART 3.—Rural outbreak of 7 cases of paralytic poliomyelitis in Vermont and 4 cases in New Hampshire occurring at the same time, showing relationships between cases and to other cases at other times and in other localities.

There are many imperfections in any statistical approach to a study of familial susceptibility to disease, chief among which are discrepancies in the data which are available or which can be obtained with reference to the past. The ideal would include not only extensive genealogies of cases and controls, but a complete record of the occurrence of the disease in them. Furthermore, in contrast with studies of conditions manifest at birth, such as albinism, completeness would require that all individuals in the genealogies had lived beyond the age at which the disease usually manifests itself, or that exposure to the environmental factor by which susceptibility is expressed has occurred. And to do all this would involve the recording of the various pertinent events as they occurred over long periods of time.

Except in hereditary conditions which are manifest early or are outstanding, as for example hemophilia or albinism, the questionnaire-history method of collecting the data is highly unsatisfactory, for the reason that a sufficient span of time, memory or knowledge is not often encompassed by the informant. The average person not only has a more or less restricted acquaintance with his family line, but an even more discrepant knowledge of the occurrence of disease in its members. The difficulties in ascertaining the facts concerning disease in relatives

of patients other than members of the same household by the questionnaire-history method are impressed on one by the frequency of a prompt "No" to the inquiry as to occurrence in relatives and the turning up, on further investigation, of even a number of cases in relatives.

Paralytic poliomyelitis has certain features which make it possible to pursue the study of its familial occurrence far beyond the simple history-questionnaire procedure. In the first place, since it is a relatively uncommon disease, familial concentration is more easily detected than in a fairly common disease. Furthermore, it occurs for the most part at an early age, so that it is not necessary to await the completion of a life span for histories of individuals, and thus the investigation can be contemporary to a greater extent than is the case in studies of disease in older persons, as for example cancer. Finally, paralytic poliomyelitis leaves permanent and easily recognized effects by which it can be identified in the individual at any time subsequent to the attack.

The following family history, not in itself particularly suggestive of any familial tendency, well illustrates the failure of the history method and success by devious methods which are made possible by the characteristics of poliomyelitis.

Three children in 1 family had poliomyelitis in Cambridge, Mass., in 1931. A few years later, when making familial studies, this family stated that there were no cases of poliomyelitis in any known relatives, no matter how distant. But on pressing the question as to lameness or crippling disease of any sort in any member of the family, the reply was, "Nothing like infantile paralysis." It was then stated that there were 2 cousins who had been crippled many years ago—the family could not remember the year. But when it was learned that these cousins lived in Cherryfield, Maine, and the family was told of the outbreak of poliomyelitis there in 1896, they were able to verify the guess that the 2 cousins became crippled that summer.

The names of the individuals coincided with the initials of 2 of the cases in "An Epidemic of Poliomyelitis" reported by Dr. J. Madison Taylor.²⁵ In this report a case was also found in a third cousin, never mentioned by the family. Thus 3 cases were verified where none was obtained by the history method.

By 1942, something had recalled to the mother of the Cambridge family that still another cousin in Cherryfield had also had the disease about the same time—was still living there and was lame. In reply to an inquiry, this individual wrote on January 12, 1942: "I did not have the disease, although my cousin may have so considered, as I have a shortening of the right leg due to osteomyelitis at age 15, about three years after the infantile paralysis epidemic."

The details of this negative history are included to show that the building up of family histories has not been a matter of including any lameness thought to be poliomyelitis, but to illustrate how, through additional verification of diagnosis, poliomyelitis has been included and lameness due to other diseases equally well excluded.

Summary. In the light of widespread dissemination of the virus, which can be held as a more or less fixed variable in the distribution of the paralytic disease, the familial aggregations of paralytic poliomyelitis reviewed in this paper are indicative of familial susceptibility to paralysis. This conclusion is warranted not so much because of the

significance of these sets of observations taken singly, but because they are found with the relative frequency which would be expected if a familial factor were operative.

The observations included here do not represent so much a pre-planned study of familial susceptibility to poliomyelitis as familial aggregations of the disease which have been encountered in the course of a general epidemiologic study. The idea of assembling such data has resulted more largely from the impressiveness of the experience of returning to a locality to see a child whose parent had been seen a good many years before as a child with the same disease. The familial aggregations reported here are enough to warrant the inclusion of similar studies in systematic epidemiologic investigations.

The intensity with which hereditary susceptibility is exhibited in the distribution of the disease, as indicated by these studies, clearly is not sufficient to afford any basis in itself for control measures, but rather forms a background for a study of the nature of individual susceptibility to paralysis; and suggests that the search for predisposing causes, long centered on immediately precedent environmental circumstances such as sanitary conditions, stresses, strains and injuries, nutrition, and so on should include conditions inherent in the constitutional makeup of the individual.

W. LLOYD AYCOCK, M.D.

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PHYSIOLOGY.

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF JANUARY 20, 1942

The Metabolism of Alanine Containing C^{13} . S. GURIN and D. WRIGHT WILSON (Department of Physiological Chemistry, University of Pennsylvania). C^{13} has all the chemical properties of ordinary carbon but its atomic mass is slightly greater. For this reason, it may be detected by a mass spectrometer whenever it is in sufficient concentration. When a compound containing sufficient C^{13} is fed, the C^{13} may be followed through the body, a procedure which has been called the feeding of tagged elements. Following tagged elements through various compounds in the body may show what changes the fed materials undergo during metabolism. The method constitutes a very valuable aid in the study of intermediary metabolism.

We have synthesized alanine containing excess C^{13} in the carboxyl group. When this alanine is fed to a phlorhizinized rat, a large amount of glucose is excreted which has been thought to come directly from the alanine. However, the glucose contains a very small amount of C^{13} . This proves that most of the sugar of the urine is formed not from the alanine fed but from other sources in the body.

Respiratory Reflexes from the Limbs. J. H. COMROE, JR, and C. F. SCHMIDT (Department of Pharmacology, University of Pennsylvania). Since Nielsen has shown that muscular exercise can increase greatly minute volume of respiration without any detectable change in arterial CO_2 , O_2 or pH, we attempted to demonstrate the presence of (a) chemoreceptors or (b) stretch receptors in the limbs capable of stimulating respiration reflexly. Repeated and varied attempts to discover chemoreceptors activated by physiologic stimuli all failed, although reflex hyperpnea was produced by injection into the femoral artery of chemical substances in concentrations beyond physiologic limits (acids, KCl, phosphate buffers pH 6.4, 6.1).

However, movements of the limbs in anesthetized dogs regularly produced hyperpnea. In 11 dogs, active movements of hind limbs (produced by anterior root stimulation) increased respiration 62%, and in 17 dogs passive movements increased respiration 50%. Mere flexion of the limbs often produced hyperpnea equal to that following rapid, alternating flexion and extension. In 70% of 33 normal human subjects, passive movements of one leg produced an increase of more than 30% in respiratory minute volume.

These changes were shown to be due to reflexes for denervation of the limbs in dogs abolished the responses even though the artery and vein were intact, and, in man, spinal anesthesia in 5 subjects greatly reduced or abolished the hyperpnea. In dogs, the receptors for this

reflex lie in or around the joint for procainization of this region abolished the response even though the leg muscles were still intact. It is probable that a large portion of the hyperpnea of muscular exercise in man is referable to reflexes arising from proprioceptors in the joints.

Dark Adaptation of Single Visual Nerve Cells. H. K. HARTLINE and R. McDONALD (Johnson Foundation and Department of Ophthalmology, University of Pennsylvania). The ability of the eye to adjust itself to widely different levels of illumination is a property inherent in its receptor elements. This property has been studied by direct observation of the discharge of nerve impulses in single optic nerve fibers from the eye of *Limulus*. During prolonged steady illumination the frequency of the discharge initiated by a visual receptor cell declines from its initially high value to a lower level. This may be ascribed in part to the bleaching of the photosensitive substance primarily responsible for sensitivity to light. The sensitivity of the receptor does not decline to zero, however, and impulses continue to be discharged at a uniform rate during very long exposure to light. This may be ascribed to a "back" reaction which keeps the supply of photosensitive material replenished. When the light is turned off this "back" reaction, unopposed by photolysis, leads to a recovery of sensitivity of the receptor cell. This recovery during dark adaptation may be followed by recording at intervals the discharges of impulses elicited by a short test flash of light. The recovery of sensitivity is initially rapid and approaches the dark adapted level asymptotically. The higher the intensity of the preceding light adaptation, or the longer its duration, the greater is the loss of sensitivity measured at the beginning of dark adaptation, and the slower the rate of recovery. Quantitatively the curves resemble those obtained by subjective measurements on human subjects.

Cell Division.* WARREN H. LEWIS (Wistar Institute of Anatomy and Biology, University of Pennsylvania). The *contractile tension* which protoplasm automatically exerts when in the gel state plays important rôles in cell division. Active cells have a superficial gel layer and a less viscous endoplasm. The gel layer, the motor organ of the cell, undergoes local changes of viscosity and corresponding local changes of contractile tension which may result in alterations of cell form, in locomotion, or in cell cleavage. During prophase, pseudopodia retract and cells tend to become spherical. Increased viscosity (increased contractile tension) of the gel layer of pseudopodia accounts for their retraction. The spherical condition is due to a uniform viscosity of the gel layer. During metaphase, the cell becomes approximately bilateral with the chromosomes in the equatorial plane. As the chromosomes move to the poles, the cell flattens in the equatorial region, due to increased contractile tension of a broad equatorial band of the gel layer which has become more viscous. Then follows the equatorial constriction, which deepens

* A motion picture demonstration.

until the cell is divided except for a connecting stalk. The constriction is due to the contraction of a narrow equatorial band of the gel layer which has become still more viscous. Changes of viscosity of cytoplasm and nucleus are probably responsible for other visible phenomena of cell division, such as the appearance of chromosomes in prophase, their movements in late prophase, metaphase and anaphase, and bleb formation during anaphase. The factors responsible for local changes of viscosity, the formation of the gel layer, and the less viscous condition of the endoplasm are unknown.

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ORIGINAL ARTICLES.

REDUCTION OF INDUSTRIAL ABSENTEEISM BY PRESEASONAL
IMMUNIZATION AGAINST CATARRHAL ILLNESS.

By M. R. BRADY, M.D.,
LONDON, ENGLAND.

MODERN war conditions exact an unparalleled strain on the physical and mental energy of industrial workers. Highly skilled men work long hours with reduced vacation, and, in many cases, with a limited range of protective foods. The detrimental effect of industrial absenteeism on the National effort needs no emphasis. Cope¹ suggested that 1,000,000 workers in Great Britain lose 1 day's work every year owing to the common cold, and Stowell,³ in Imperial Chemical Industries, reported that of 75.2% absentees from all illness, 51.6% was due to catarrhal conditions.

Before describing the methods used in an endeavor to reduce absenteeism due to catarrhal illness in a large industrial undertaking, it would be well to refer to previous work in the same field. In 1920 Leishman had 15,624 men in the British Army inoculated with mixed anti-influenza vaccine containing Pfeiffer's bacillus, pneumococcus and streptococcus. Of those inoculated the incidence of attack of influenza was 14.1 per 1000 as against 47.3 per 1000 for a group of 45,520 uninoculated. Pulmonary complications were 1.6 per 1000 as against 13.3 for the uninoculated.

In 1931, Stowell,³ using an antigen somewhat similar to that used in this experiment, inoculated part of the staff of Imperial Chemical Industries. He reported that the percentage of inoculated persons who lost time owing to catarrhal condition as 35.3, while the corresponding percentage for uninoculated was 51.6%.

In recent years research has been focused on the virus field. The work of Francis in America was confirmed by Smith, Andrews and Laidlaw in England in 1933. The etiology of that collection of diseases which was labelled "flu" seemed to be settled, until later it

was discovered that the clinical influenza did not always produce the virus when infected material was injected into ferrets. [This is chiefly significant as emphasizing the difficulty in differentiating "clinical" from what is now widely accepted as the real disease, especially in sporadic cases.—Ed.] The Medical Research Council¹ reported, however, that in the 1936-37 influenza epidemic no difficulty was experienced in recovering the virus from typical cases, the ferret being employed for the purpose. American workers in 1934 reported that the mouse could be infected with ferret-passage virus. The infection of a mouse direct with human material was not successful. British and American workers have confirmed that different strains of influenza virus (A and B types) exist and this is probably responsible for the disappointing results experienced in employing the virus for prophylactic immunization. Reviewing this report and previous work, the British Medical Journal in 1938² stated "So far as the effective immunisation of man is concerned, no great advance is reported."

Stock bacterial vaccines prepared for the prevention of influenza and the common cold have, in many cases, given disappointing results, and this in turn is probably due, at least in part, to the multiplicity of strains of the microorganisms associated with the common cold, such as the streptococcus. American workers have typed several hundred strains. [According to recent concepts, a mild virus infection prepares the way for bacterial sequelæ that are the causes for "absenteeism" in the case of the common cold, at least; in real influenza their effect seems to be less requisite, though by no means clearly defined as yet. For the common cold, however, there seems to be adequate rational basis for the prophylactic use of bacterial vaccines.—Ed.]

Bearing these factors in mind, Stowell,³ in 1931, used what he described as a "mass autogenous vaccine" when inoculating the Staff of Imperial Chemical Industries, and I have since employed similar methods in several large industrial undertakings.

Methods. The endeavor now reported was carried out in Pye Radio Works, Cambridge. The factory employed over 1800 people and 950 of these volunteered for inoculation. Before the vaccine was prepared several visits were made to the factory and cultures were taken from those suffering from acute colds. Warmed culture media was used and put directly into an incubator. Those suffering from colds immediately before or during the administration of the inoculations were regarded as carriers and treated with autogenous vaccines. Cultures were also taken from the more susceptible persons in the factory, and in this way a great variety of local strains was obtained. In the manufacture of the mass vaccine scrupulous attention was paid to bacteriologic details. Apart from the numerous strains of microorganisms isolated at the factory, we were fortunate at having in the Laboratories, many strains from other sources. Infinite care was taken in typing the different microorganisms, the aim being to make the finished vaccine as polyvalent as humanly possible. Those who volunteered for inoculation were divided into three groups:

- A. Those who were subject to occasional colds but were otherwise normal.
- B. Those who were extraordinarily susceptible to colds during the winter.
- C. Those having respiratory affections or colds.

Those in group A were inoculated with the mass vaccines containing strains of the following organisms: staphylococci, streptococci, micrococci, pneumococci, Pfeiffer's bacillus, Friedländer's bacillus. Four doses were given at weekly intervals, the first dose containing 125,000,000 micro-organisms and the final 1,000,000,000.

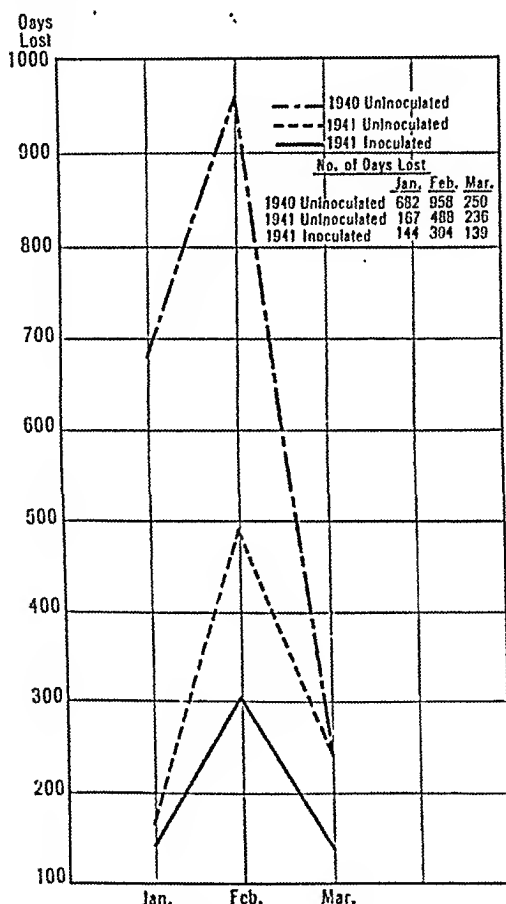


CHART 1.—Absenteeism per 1000 in three groups of employees.

The initial dose for the susceptible in Group B was one-tenth of that given to the normals in Group A. The treatment for both consisted of 6 doses, the final dose being 1,000,000,000.

Those in Group C were treated with autogenous vaccines, 8 to 12 doses being administered according to results observed.

Some of those in Groups A and B contracted colds during the inoculations and were transferred to Group C and treated with autogenous vaccines, the new strains being added to the mass vaccine.

Doses were carefully graduated in order to avoid reactions and it was found generally that those who did not react to the initial dose finished the course without incident. Those in Groups A and B who reacted to the first dose were given a reduced dose on one-tenth the strength for their next injection and put on a 6-dose course.

The results of the inoculations, completed in January, 1941, were carefully recorded by the factory matron and works manager. Before commenting on results, it should be mentioned that if inoculation is offered to a large group of people, those predisposed to colds will naturally be more inclined to come forward and this undoubtedly affects the results when comparing inoculated and non-inoculated groups. The first results caused disappointment as they recorded the incidence of "colds" as unfavorable to the inoculated group, the final figures in "C" not being available until later:

TABLE 1.—COLDS REPORTED JANUARY-MARCH, 1941.

	Inoculated group.	Uninoculated group.
Number in group	950	913
A. Colds reported	217	123
B. Cases of influenza	47	55
C. Days lost, colds and "flu."	558½	814½

Before interpreting these figures, it should be noted that those in the inoculated group were instructed to report the slightest sign of a cold, while those who refused inoculation would, of course, be less inclined to report. Nevertheless, the figures are worth recording as they clearly indicate that those inoculated contracted an undiminished number of colds and influenza, but the severity of the attack was much less than those who were not inoculated. This is clearly shown in "C."

The number of days lost in both groups in the factory were recorded and absenteeism was expressed as a percentage of the total possible working days:

TABLE 2.—ABSENTEEISM FROM COLDS AND INFLUENZA IN UNINOCULATED AND INOCULATED GROUPS FROM JANUARY TO MARCH, 1941.

	Inoculated group.	Uninoculated group.
Number in group	950	913
Total possible working days	72,200	69,388
Number of days lost	558	814
Absenteeism773%	1.173%
Reduction in number of days lost	34.1%	

It will be noted that the inoculated group shows a reduction of 34.1% in the number of days lost, compared with those who refused inoculation.

The figures for absenteeism were recorded in the factory over the same period in the previous year. Although there were 660 less employees than in 1941, the actual number of days lost was much greater in 1940. It should, of course, be remembered that nationally no epidemic was reported in 1941.

TABLE 3.—TOTAL ABSENTEEISM IN FACTORY FROM COLDS AND INFLUENZA IN JANUARY TO MARCH, 1940, COMPARED WITH 1941.

	1940.	1941.
Number in factory	1197	1863*
Total possible working days	90,972	141,588
Number of days lost	2245	1372
Absenteeism	2.468%	.969%
Reduction in number of days lost	60.7%	

* Of these, 950 were immunized.

Absenteeism was recorded at the factory each month from January to March and it was found that the peak was reached in February in both inoculated and uninoculated groups. Comparing these groups with the 1940 uninoculated group, it was found that although the rate of absenteeism per 1000 was much greater in 1940 than in the inoculated and uninoculated groups in 1941, the curve of absenteeism in all three groups was similar in these months.

Conclusions. In a large chemical factory 950 persons were inoculated with a mixed anti-influenza and common cold vaccine containing local strains. Absenteeism due to catarrhal illness in this group compared with an uninoculated group showed a reduction of 34.1% in the number of days lost.

The total absenteeism from catarrhal illness in the factory in 1941 was compared with that of the previous year and a substantial reduction in the number of days lost was recorded.

The rate of absenteeism per 1000 was recorded for three groups from January to March in 2 years and the peak absenteeism from catarrhal illness in each group was found to occur in February.

I must express my thanks to the management of Pye Radio Ltd. for the facilities placed at my disposal, and for the accurate way in which the results were recorded. I am also indebted to the technical staff of The Antigen Laboratories for their arduous work in the typing of many hundreds of microorganisms and the preparation of the vaccines.

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INFARCTION IN HEART DISEASE.

By CURTIS F. GARVIN, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, WESTERN RESERVE UNIVERSITY SCHOOL OF MEDICINE; VISITING PHYSICIAN, MEDICAL SERVICE, CLEVELAND CITY HOSPITAL, CLEVELAND, OHIO.

(From the Department of Medicine of Cleveland City Hospital and the Western Reserve University School of Medicine.)

THE paucity of information concerning the incidence of embolic manifestations in heart disease has been pointed out by Weiss and Davis.¹ Since absolute differentiation between vascular embolism and thrombosis was not always possible, they presented embolic manifestations as infarcts. Believing that "rheumatic heart disease, more than any other type of heart disease, is responsible for embolic manifestations," they analyzed 164 cases in which death was caused by rheumatic heart disease. They found infarction of one or more organs in 73 cases, an incidence of 45%. In 41 instances, one; in 22 instances, two; and in 10 instances, three or more organs were

involved by single or multiple infarcts. The organs involved were: lungs, 31; brain, 28; kidneys, 25; spleen, 18; extremities, 10; intestines, 5; and liver, 1.

The present study deals with the incidence and the factors influencing the occurrence of infarcts in 771 consecutive autopsied adult patients in whom heart disease was the chief cause of death. These cases occurred in 6285 consecutive autopsies done at the Cleveland City Hospital from January, 1930, to July, 1939, inclusive.

Three hundred and fifty-four (45.9%) of the 771 patients had one or more infarcts in the lungs, brain, kidneys, spleen, extremities and/or intestines. The incidence of infarction of one or more of these viscera in the various types of heart disease is shown in Table 1. Subacute bacterial endocarditis was most frequently associated with infarction (80%); coronary artery disease with myocardial infarction about 60%. Coronary artery disease without myocardial infarction and rheumatic heart disease were about alike (approximately 50%). The incidence of infarction in hypertensive heart disease and syphilitic heart disease was about 40%, and this complication was uncommon in cor pulmonale.

TABLE 1.—THE NUMBER OF CASES OF THE VARIOUS TYPES OF HEART DISEASE AND THE NUMBER AND PER CENT OF CASES HAVING ONE OR MORE INFARCTS IN THE LUNGS, BRAIN, KIDNEYS, SPLEEN, EXTREMITIES, AND/OR INTESTINE.

Type of heart disease.	No. of cases.	No. with infarcts.	%.
Subacute bacterial endocarditis	30	24	80.0
Coronary artery disease with myocardial infarctions*	133	79	59.4
Coronary artery disease without myocardial infarctions*	94	49	52.1
Rheumatic heart disease	116	56	48.3
Hypertensive heart disease	147	62	42.2
Syphilitic heart disease	67	25	37.3
Cor pulmonale	50	5	10.0
Hypertensive heart disease complicated by various types of heart disease	15	5	33.3
Acute bacterial endocarditis	13	9	69.2
Hypertensive heart disease and rheumatic heart disease	13	8	61.5
Coronary artery disease without myocardial infarction complicated by various types of heart disease	10	4	40.0
Calcific stenosis	8	3	37.5
Thyroid heart disease	8	0	0.0
Obliterative pericarditis	7	0	0.0
Tuberculous pericarditis	7	0	0.0
Coronary artery disease with myocardial infarction complicated by a variety of types	5	5	100.0
Undiagnosed	34	14	41.2
Miscellaneous	14	6	42.9
Total	771	354	45.9

* Whether there was associated hypertensive heart disease or not made no appreciable difference.

The frequency with which the lungs, brain, kidneys, spleen, extremities and intestines were infarcted in the 771 cases of heart disease is shown in Table 2; the order of decreasing frequency being lungs, 28.7%; kidneys, 17%; spleen, 11.7%; extremities, 2.6%; and intestines, 1.7%. There was infarction of the brain in 76 of 432 examinations (17.6%). The highest incidences of infarction occurred in subacute bacterial endocarditis (kidney, 70%; and spleen, 66.7%). These figures are statistically highly significant* in comparison with the average of the remainder of the cases.

TABLE 2 — THE INCIDENCE OF INFARCTION OF THE LUNGS, BRAIN, KIDNEYS, SPLEEN, EXTREMITIES AND INTESTINES IN THE VARIOUS TYPES OF HEART DISEASE.

Type of heart disease.	Lungs.		Brain.		Kidney.		Spleen.		Extremities.		Intestines.		
	No. infarcts.	%.	No. examined.	No. infarcts.	%.	No. infarcts.	%.	No. infarcts.	%.	No. infarcts.	%.	No. infarcts.	%.
Subacute bacterial endocarditis, 30 cases.	5	16.7	16	5	31.2	21	70.0	20	66.7	2	6.7	0	0.0
Coronary artery disease with myocardial infarction, 133 cases*.	45	33.8	80	18	22.5	32	24.1	19	14.3	11	8.3	3	2.3
Coronary artery disease without myocardial infarction, 94 cases*.	29	30.9	56	17	30.4	15	16.0	7	7.4	4	4.3	2	2.1
Rheumatic heart disease, 116 cases.	38	32.8	56	11	19.6	24	20.7	14	12.1	1	0.9	4	3.4
Hypertensive heart disease, 147 cases.	45	30.6	79	12	15.2	14	9.5	9	6.1	1	0.7	3	2.0
Syphilitic heart disease, 67 cases.	20	29.9	37	4	10.8	2	3.0	3	4.5	0	0.0	0	0.0
Cor pulmonale, 50 cases.	2	4.0	36	2	5.6	0	0.0	0	0.0	0	0.0	0	0.0
Remainder, 134 cases.	37	27.6	72	7	9.7	23	17.2	17	12.7	1	0.7	1	0.7
Total, 771 cases.	221	28.7	432	76	17.6	131	17.0	90	11.7	20	2.6	13	1.7

* Whether there was associated hypertensive heart disease or not made no appreciable difference.

The number of infarctions in the cases of the various types of heart disease is shown in Table 3. Twenty-seven and one organ only, 13.5%.

* Whether there was associated hypertensive heart disease or not made no appreciable difference.

The number of infarctions in the cases of the different types is shown in Table 3. Twenty-seven and a tenth per cent had infarcts in one organ only, 13.5% in two only, and 5.3% in three or more organs. The high incidence of infarction of multiple viscera in subacute bacterial endocarditis is noteworthy, 66.6% having two or more organs infarcted. This is a highly significant difference from the average of the other types of heart disease. There was no association between infarction and sex, color, age, or the weight of the heart. There was a tendency for patients having more than one episode of heart failure and for patients with auricular fibrillation to have a higher incidence of infarction but in no type of heart disease was the difference statistically significant.

* In this article, the term "significant" refers to a difference which could be produced by chance in less than 5% of trials as demonstrated by application of the chi square test; "highly significant" refers to a difference so great that it could be produced by chance in less than 1% of trials, again as demonstrated by application of the chi square test.

TABLE 3.—THE NUMBER OF CASES OF VARIOUS TYPES OF HEART DISEASE, AND THE NUMBER AND PER CENT OF THESE HAVING INFARCTS IN ONE ONLY, TWO ONLY, AND THREE OR MORE ORGANS. THE ORGANS CONSIDERED ARE THE LUNGS, BRAIN, KIDNEYS, SPLEEN, INTESTINES AND EXTREMITIES.

Type of heart disease.	Infarction of one organ only.		Infarction of two organs only.		Infarction of three or more organs.	
	No.	%.	No.	%.	No.	%.
Subacute bacterial endocarditis, 30 cases	4	13.3	13	43.3	7	23.3
Coronary artery disease with myocardial infarction,* 133 cases	46	34.6	20	15.0	13	9.8
Coronary artery disease without myocardial infarction,* 94 cases	28	29.8	18	19.1	3	3.2
Rheumatic heart disease, 116 cases	32	27.6	15	12.9	9	7.8
Hypertensive heart disease, 147 cases	43	29.3	16	10.9	3	2.0
Syphilitic heart disease, 67 cases	21	31.3	4	6.0	0	0.0
Cor pulmonale, 50 cases	5	10.0	0	0.0	0	0.0
Remainder, 134 cases	30	22.4	18	13.4	6	4.5
Total, 771 cases	209	27.1	104	13.5	41	5.3

* Whether there was associated hypertensive heart disease or not made no appreciable difference.

Summary. Of 771 consecutive adult autopsied patients dead of heart disease, 354 (45.9%) had one or more infarcts in the lungs, brain, kidneys, spleen, extremities and/or intestines. Subacute bacterial endocarditis was the type of heart disease most frequently associated with infarcts of the viscera, 80% of the cases showing this complication. In coronary artery disease with myocardial infarction, about 60% of the cases had one or more infarcts in the lungs, brain, kidneys, spleen, extremities and/or intestines. Coronary artery disease without myocardial infarction and rheumatic heart disease were about alike, approximately 50% of the cases showing one or more infarcts. The incidence of infarction in hypertensive heart disease and syphilitic heart disease was about 40%, and this complication was uncommon in cor pulmonale.

Of the 771 cases, the lungs were involved by infarction in 28.7% of the cases, the kidney 17%, the spleen 11.7%, the extremities 2.6% and the intestines 1.7%. There was infarction of the brain in 17.6% of 432 examinations. The highest incidences of infarction occurred in subacute bacterial endocarditis (kidney, 70%; and spleen, 66.7%).

The percentage of cases with one organ infarcted was 27.1, with two organs infarcted 13.5, and with three or more, 5.3. The highest incidence of infarction of multiple viscera was in subacute bacterial endocarditis, 66.6% of the cases having two or more organs infarcted.

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HEMOGLOBIN AND PLASMA PROTEINS: THEIR PRODUCTION,
UTILIZATION AND INTERRELATION.*

BY G. H. WHIPPLE, M.D.,

PROFESSOR OF PATHOLOGY, THE UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE
AND DENTISTRY, ROCHESTER, N. Y.(From the Department of Pathology, The University of Rochester School of Medicine
and Dentistry.)

It is a truism to say that protein production is a very complex reaction which must depend upon cellular activities. In the study of hemoglobin and plasma proteins, we have used the stimulus of depletion. In all this work we have been impressed by the alacrity with which the body can supply a needed protein. This suggests *reserve stores* of protein building material and a ready "give and take" between protein stores under the stress of emergencies, *e. g.*, depletion or fasting. We have used the term "*dynamic equilibrium*" to indicate this ebb and flow of protein between cells and plasma which goes on so readily with little delay and with little or no loss of nitrogenous materials.

Recently Madden and Whipple²³ have reviewed much of the experimental work related to the *plasma proteins*. A general review does not seem appropriate at this time—rather a presentation of work and conclusions published from this laboratory, attempting to mold all these observations into a single thesis which may have some interest to the physician who is concerned with the treatment and study of anemia, protein deficiencies, shock, and tissue injury.

Methods. It is not necessary to give details which are published elsewhere but it is well to emphasize that all these observations relate to dogs which are healthy and active but present some departure from the strictly normal dog—anemia, plasma depletion, bile fistula, Eck fistula. Anemia is produced by withdrawal of blood from veins maintaining the anemia level relatively constant, usually 6 gm. hemoglobin per 100 cc. blood. Plasma depletion is effected by bleeding followed by a return of washed red cells to maintain the red cell hematocrit close to 45% and the plasma protein level about 4 gm. per 100 cc. Plasma depletion and anemia are combined in some experiments. The bile fistula dogs drain all bile from the common duct either into a sterile bag or into the renal pelvis and urine. They can be kept in perfect health for years on the proper regimen.²⁷ The Eck fistula diverts all portal blood to the inferior vena cava and presents an atrophic liver which at times may present interesting abnormalities in plasma protein production. These dogs with proper care and diet live in health for years. These dogs are essentially *biologic testing machines* by which we can measure the capacity of the body to produce hemoglobin or plasma proteins or both, the production of bile pigment as related to hemoglobin, or the output of various plasma proteins as influenced by a subnormal liver (Eck fistula).

Hemoglobin Production. It has been well established that hemoglobin production in anemia can be controlled by diet^{1b}—more

* A considerable part of this paper was presented in the Sixteenth Pasteur Lecture given before the Institute of Medicine of Chicago, November 28, 1941.

specifically that iron and protein stores or intake are the essential factors. It is not difficult to show that strict control of the *iron intake* will limit the hemoglobin production in the standard anemic dog.^{42a} Also by limiting the *protein intake* in anemia the hemoglobin production can be reduced.¹¹ The *pigment radicle* of hemoglobin is thrown away when red cells are destroyed or hemoglobin introduced into the circulation in bile fistula dogs.¹⁷ This peculiar response has been carefully studied and though a wasteful reaction must be accepted as a fact—an indication that the dog can produce the pyrrol ring with great ease.¹⁷

As anemia can be controlled by diet and iron in the healthy dog, it is probable that the same holds true for anemia due to blood loss in man (gastric ulcers, uterine bleeding, hemorrhoids and so forth). These *diet factors* have been noted previously^{41a} but it may be stated that cooked or raw liver heads the list of potent food materials, then come kidney, stomach and pancreas. Meats are below these visceral proteins. Prunes, apricots and peaches are unusually potent and the potency resides largely in the ash.⁸ Vegetables, dairy products, fish and many fruits are relatively inert for new hemoglobin production in anemia.

Minerals have been studied in relation to hemoglobin production in anemia. Iron is a part of the hemoglobin molecule and obviously must be a factor. One gram of hemoglobin contains 3.5 mg. of iron and when colloidal iron is given by vein to a standard anemic dog, we expect to recover 1 gm. new hemoglobin for every 3.5 mg. iron injected. When iron is fed, the story is very different and the absorption of iron at best is poor and when there is no need for iron the intestinal mucosa does not accept iron salts.¹³ We have been unable to detect any constant difference in soluble forms of iron as to their usefulness in anemia in dogs—ferrous or ferric salts, iron oxide, or reduced iron, all react alike in the dog and we suspect the same is true for man. *Cobalt* has been much studied⁹ but appears to have little effect upon hemoglobin production. *Copper* has been studied in many laboratories^{6,8,14} and under certain conditions does have an effect upon hemoglobin production in experimental anemia.

When hemoglobin wears out or dies in the circulation as the red cells go to pieces, we may ask is there a resurrection? The answer is probably Yes. We know that the iron is treasured by the body and only traces escape by way of bile and urine.¹² The *globin* is saved in large part and probably is used over again to form new hemoglobin or to supply some other protein needs of the body. Foreign globin or hemoglobin (goose, sheep, horse) can be utilized to form new hemoglobin³⁵ when given by vein to a standard anemic dog—indicating a significant cleavage and recasting of the introduced globin into dog globin. This turnover of introduced or destroyed hemoglobin into new hemoglobin is very rapid and requires only a few hours or days depending upon the amount of

hemoglobin involved and severity of stimulus (depletion). We suspect that globin in an emergency should contribute to the building of new plasma protein in a plasma depleted dog but can get no evidence for such a response. The metabolic pattern does not allow this but does permit the fasting dog to utilize introduced hemoglobin or hemoglobin digests to supply other protein requirements.

Hemoglobin production may be modified in various ways in these standard anemic dogs. *Infection* may profoundly change the expected response to liver feeding—in fact the hemoglobin output may fall to zero instead of the expected 90 to 100 gm. hemoglobin.^{33a} This has been observed in association with endometritis and sterile abscess production. *Nephritis* in the late stages causes only moderate impairment of hemoglobin production.^{42c} The Eek fistula usually permits normal hemoglobin production. The bile fistula¹⁶ however cuts the expected hemoglobin production by 50% and this is not wholly an absorption phenomenon.

Fasting experiments yield valuable information and have been carefully studied in this laboratory. Given a standard anemic dog fed an optimum dose of iron with sugar and fat but no protein, we expect 40 to 50 gm. new hemoglobin produced each week for several weeks. Obviously the protein (globin) must be formed to a considerable degree from body stores presumably held in cells in some protein form—a rather extensive shift of important protein material from various body depots into red cells. Such dogs show less nitrogen in the urine especially in the urea-ammonia fraction,^{5b} as compared with normal non-anemic controls. This would indicate that the precursors of the urea were utilized to some extent in the building of the new hemoglobin under these conditions—a reaction of conservation.

Plasma protein production at the moment is of special interest to physicians because of the recent appreciation of the value of plasma in the treatment of various shock conditions. If new plasma protein can be formed rapidly within the body, this is of obvious advantage over the introduction of plasma from outside, which is troublesome and expensive. After an acute emergency is tided over with plasma injections, a continuing supply may come from the body if we supply proper material other than plasma by vein.

The old idea that plasma proteins are inert colloids which have to do with fluid equilibrium and little else is a real handieap to medical thought. It is responsible for the use of acaemia and other inert gums in shock conditions. I know of no reason why these foreign materials should be administered and many reasons why they should never be utilized in the clinic; considerable amounts of acaemia will cause liver storage, actual damage and impaired liver function.¹⁵

Plasma proteins are in *dynamic equilibrium* with body cell proteins. It was demonstrated years ago¹⁹ by Holman, Mahoney and

Whipple that the protein requirements of the dog for weeks at a time could be supplied by plasma protein given by vein during protein fasting. Moreover, tissue repair is furthered and tissue injury is prevented when plasma proteins are administered or fabricated by the depleted dog—all good reasons why plasma proteins are so helpful in shock where tissue injury is often an important factor.

The *liver* is believed to be of primary importance in the production of plasma protein, as discussed elsewhere.²³ Much interest recently has been centered on *prothrombin* because of its relationship to bleeding in various diseased conditions. This plasma protein is formed in the liver³⁶ and because of its precipitation reactions was at first placed in the globulin fraction. More recent work with electrophoresis, however, indicates that prothrombin belongs in the albumin fraction.³⁰ If this work is confirmed this gives clear evidence that an important *albumin* is formed in the liver. It is well established that the important *globulin* fibrinogen is produced only in the liver.

Emergency production of plasma protein depends upon reserve protein stores and the intake of protein or protein derivatives either by mouth or by vein. Protein reserves²³ suitable for plasma protein production may be depleted and completely exhausted by fasting, long-continued protein-free diets, or by plasma depletion (removal of blood and return of washed red cells). Protein reserves relate to the previous diet periods and may be very large after abundant protein intake.^{2,24} It may require many weeks to deplete this protein reserve, but, once depleted, the dog can scarcely produce any new plasma protein other than from protein or protein digests or proper combinations of amino-acids given by mouth or by vein. It is possible that the 1 to 4 gm. plasma protein which are formed by the depleted dog during a protein-free week may be derived from a capture of certain split products which would otherwise appear in the urea-ammonia fraction of the urinary nitrogen.

Food proteins vary somewhat in their capacity to form new plasma protein in depleted dogs. *Serum* stands at the head of the list and it requires only 3 gm. of serum protein by mouth to produce 1 gm. new plasma protein in the depleted dog. Other food proteins require 4 to 7 gm. by mouth to produce 1 gm. new plasma protein (Table 1). In general, food proteins are better used when given alone and in moderate amounts. Larger protein intake yields a lower per cent return of plasma protein. The experiments of Weech⁴⁰ dealing with albumin and of McIniek, Cowgill and Buraek²⁷ have been reviewed recently.²³

Table 1 shows how much variety there is in the hemoglobin production of the anemic dog and in the plasma protein production in the plasma depleted dog. The ceiling for hemoglobin production is easily reached and for a 10-kilo dog is about 70 gm. hemoglobin per week on a favorable diet of liver plus iron. The capacity of the

plasma-depleted dog to form plasma protein is even greater; but the technical difficulties make it impossible to establish a ceiling for plasma protein production. For this reason a plus sign is added to the figures for plasma protein production in Table 1. Consequently, the protein intake is held down in the plasma-depleted dog and the protein is always somewhat better utilized when given in small or moderate amounts. There are conspicuous differences in the food factors (Table 1) and the related production of hemoglobin and plasma protein—for example, compare liver, serum and salmon bread. Liver is best to form hemoglobin and well utilized for plasma protein production. Serum is best used to produce plasma protein but not particularly well used for hemoglobin production. Casein and salmon bread are very poor producers of hemoglobin but excellent for plasma protein production.

TABLE 1.—COMPARISON OF HEMOGLOBIN PRODUCTION AND PLASMA PROTEIN PRODUCTION.

	By standard anemic dog.		By standard plasma—depleted dog.	
	Total net hemoglobin, av. output production, 1 week.	Ratio, protein intake to hemoglobin output.	Total net plasma protein production, 1 week.	Ratio, protein intake to plasma protein output production.
Liver (pig)	50	8/1	65+	6/1
Kidney (pig)	35	9/1	20+	5/1
Heart (beef)	25	14/1	50+	10/1
Spleen	18	22/1	20+	10/1
Pancreas	15	29/1	20+	20/1
Stomach (pig)	11	31/1	10+	15/1
Serum (ox)	15	10/1	70+	3/1
Casein	14	42/1	45+	8/1
Egg white	15	8/1	40+	5/1
Yeast	4	14/1	25+	5/1
Soy bean	5	35/1	20+	7/1
Salmon bread	5	50/1	50+	4/1

Amino-acids may contribute to plasma protein formation, as they do to hemoglobin building in anemia.^{42d} Cystine appears to be one of the key amino-acids in plasma protein building.²⁵ Experiments are in progress in this laboratory to show what aggregation of pure amino-acids added to a protein-free diet are required to produce an abundance of new plasma protein in the plasma-depleted dog.

Protein digests are of considerable importance and should be used to replace much of the plasma now used so freely in the clinic. Protein digests (casein) can bring about much new plasma protein formation in the depleted dog.²⁶ Various digests must be tested in this fashion and subsequently used cautiously in the clinic. Eventually satisfactory digests will be prepared for clinical use—the digest should promote plasma protein building and nitrogen balance, it must be non-toxic, readily sterilized, and should be inexpensive. Digests will be ideal to supplement the use of dried human plasma or replace it after the acute emergency. Digests should be very useful in human cases of gastro-enteritis where the plasma proteins are seriously depleted.

When plasma protein is produced in the depleted dog, the A/G ratio (albumin-globulin) may be modified and in general tends to fall—that is, the globulin tends to increase more than the albumin. Meats and visceral proteins tend to increase the output of albumin and certain other foods (*e. g.*, rice and potato) tend to increase the globulin fraction. Soy bean protein appears to good advantage and is used very promptly to produce plasma protein and favors the production of albumin.

When plasma is given by vein to supply the protein requirements of a fasting dog, we note no change in the A/G ratio indicating that these proteins are used up in the normal ratio. Taken together with observations above, it would appear that many changes in the A/G ratio are due to *production* factors rather than to *use* of one protein in preference to another in the body economy.

Plasma protein production may be seriously disturbed by infection (abscess) in spite of adequate protein intake. Liver abnormalities,^{4,39} liver disease, and the Eck fistula,²¹ may depress plasma protein production and bring about hypoproteinemia in man or animal. Presumably the liver cells which produce the plasma protein are destroyed or injured with impairment of their productive activity.

In the anemic iron-depleted dog certain standard diet factors have little influence upon hemoglobin building (*e. g.*, salmon bread) but in the plasma protein-depleted dog this same food may favor abundant production of new plasma protein (Table 1). With this information at hand we believed that in a dog *both anemic and plasma depleted* we could influence the protein flow toward hemoglobin by one food factor or toward plasma protein by another food. These doubly depleted dogs are not easily fed and controlled but we have had success with dogs fed iron and a relatively low protein diet.³⁴ By bleeding alone it is possible to attain *anemia plus plasma protein depletion* (Table 2). To our surprise we observed that *such dogs always produce more hemoglobin than plasma protein* no matter what diet protein is used. The ratio is 40% to 70% as much plasma protein as hemoglobin even when salmon or salmon bread is fed. The depletion stimulus to form both hemoglobin and plasma protein is present but the output always shows a surplus of hemoglobin. The food protein is well utilized and from an intake of 100 gm. protein by mouth we note the return as new hemoglobin and plasma protein of 20 to 30 gm.

Table 2 presents in condensed form a long period (69 weeks) during which the dog remained in good clinical condition, gained weight and ate the limited diet. This dog (Table 2) was continuously anemic 2 years before Table 2 begins. This experiment is a good sample of many others reported elsewhere.³⁴ Periods 4 and 5 deserve particular attention. Long periods of 13 and 14 weeks present identical diets except for iron added in Period 5. The hemoglobin output increases due to the iron, as was to be expected, but the

plasma protein increases at the same rate and there is no change in the plasma protein level.

TABLE 2.—SIMULTANEOUS PRODUCTION OF HEMOGLOBIN AND PLASMA PROTEIN IN ANEMIA AND HYPOPROTEINEMIA DUE TO BLEEDING.

Dog 37-81.

log 37-81.

Period.		Iron added daily (kg.). (mg.).		Protein intake.		Protein output.				Production ratio, plasma protein to hemoglobin (%)	Protein output to intake, %.
						Hemoglobin.		Plasma protein.			
						Level (gm. per 100 cc.).	Output per wk. (gm.).	Level (gm. per 100 cc.).	Output per wk. (gm.).		
No.	Wks.	Wt. (kg.).		Type.	Weekly (gm.).						
1	7	11.0	0	Liver	147	6.4	12.1	5.6	7.0	58	13
2	4	12.8	200	Liver	147	7.2	24.0	5.5	16.1	67	27
3	8	Interval							
4	13	15.2	0	Liver	224	6.6	22.7	5.7	15.5	68	17
5	14	15.7	200	Liver	228	7.6	33.3	5.8	21.0	63	24
6	2	14.2	200	Low protein	3	7.0	28.3	4.4	16.1	57	
7	5	14.6	200	Liver	228	7.0	23.5	4.9	14.2	60	17
8	4	15.2	200	Salmon	208	7.6	31.0	5.2	19.4	63	24
9	5	14.9	200	Kidney	154	7.5	25.9	5.2	16.5	64	28
10	3	13.5	200	Salmon bread	155	6.9	25.0	4.8	12.6	50	24
11	4	13.6	200	Liver	193	7.7	30.7	5.5	18.0	59	25

Period 6 is of much interest because during a diet practically protein-free we note the expected large hemoglobin output^{5a} but also considerable new plasma protein production. This latter is to be explained in large part as related to the sharp drop in plasma protein levels, indicating a strenuous depletion of circulating plasma protein and related reserve stores.²³

Period 7 is precisely like Period 5 as to diet and iron intake but the hemoglobin and plasma protein outputs are distinctly less. We may choose to explain this on the basis of repletion of reserve stores exhausted during Period 6 and we note gain in weight.

Period 8 shows that canned salmon supplemented with iron is well utilized to form both hemoglobin and plasma protein. In fact, the output is almost equal to Period 5 with liver replacing the salmon muscle. The utilization of protein in both periods is 24%.

Period 9 (Table 1) shows that kidney is also well used. The protein intake is about 50 gm. less than for salmon and the hemoglobin and plasma protein are correspondingly decreased in output. The ratio of plasma protein to hemoglobin remains unchanged as does the concentration of plasma protein in the circulation.

Period 10 shows that salmon bread^{42b} is used as well as the other proteins by this dog (bread protein = grain and salmon muscle). We felt confident that there would be an increase in the output of plasma protein as compared with hemoglobin but the reverse is true. We note a drop in the plasma protein levels and ratio of plasma protein to hemoglobin production. In the simple anemia experiments the salmon bread diet produces very little new hemoglobin unless there is a large iron supplement. In plasmapheresis the salmon bread is very well used to produce abundant new plasma protein. In this experiment the dog uses the proteins in salmon bread very well—protein output 24% of the intake.

Period 11 with a shift back to liver shows an increase of hemoglobin in proportion to the protein fed but even more increase in plasma protein output.

Prolonged hypoproteinemia or anemia *per se* causes no damage to the body mechanism responsible for the production of plasma protein and hemoglobin. The dogs can be kept in good health for years. Yet they are not equal to normal controls in their resistance to *infection and intoxication*. We found that dogs anemic for years were more susceptible to respiratory infections, to endocarditis, to endometritis, and to various types of enteritis. Plasma-depleted dogs are even more susceptible to infections and many of the dogs used in the early experiments died of abscesses, septicemia, endocarditis and related conditions. These dogs are also very susceptible to *intoxication* by certain drugs and their resistance to chloroform poisoning may be less than one-fourth of normal. These dogs are also more susceptible to arsenicals (*e. g.*, salvarsan) and this susceptibility is removed by adequate protein feeding.²⁸

TABLE 3.—METHIONINE PROTECTION AGAINST CHLOROFORM POISONING AND LACK OF PROTECTION OF TRYPTOPHANE, PHENYLALANINE, ISOLEUCINE, ASPARTIC ACID, VALINE AND LYSINE.

EXPERIMENT 18 (Dog 39-130). Low protein diet for 11 weeks.

Hours before or after chloroform.	Plasma protein, gm. per 100 cc.	Fibrinogen, mg. per 100 cc.	Icterus index.	Food consumed, %.	Clinical condition.
0	5.39	478	0	Fast	Normal
(Chloroform anesthesia—40 minutes, preceded by methionine intravenously, 2.5 gm. 5 hours before and 2.3 gm. 2 hours before.)					
24	5.35	440	0	60	Good
48	5.21	419	0	15	Good
72	5.19	403	0	85	Normal
120	5.40	425	0	50	Normal

EXPERIMENT 19 (Dog 39-130). Low protein diet continued for 3 weeks.

0	4.80	375	0	Fast	Normal
(Chloroform anesthesia—20 minutes, preceded by amino-acid mixture 21 hours and 4 hours before, by stomach tube.)					
24	165	9	10	Intoxicated
44	Death—chloroform poisoning.				

The lowered resistance to chloroform poisoning related to hypoproteinemia can be readily demonstrated and Table 3 is a good example.²⁹ A well-fed normal dog will tolerate an hour's chloroform anesthesia with little evidence of intoxication; but after plasma depletion it will show fatal intoxication with extensive liver necrosis due to 15 to 20 minutes' chloroform anesthesia. This susceptibility of the plasma-depleted dog can be promptly removed by large protein feedings or considerable amounts of plasma given by vein. Furthermore, *methionine* (or cystine to a less degree) will protect the plasma-depleted dog against 40 minutes' chloroform anesthesia, and other non-sulphur-containing amino-acids are inert in the same type of experiment (Table 3). *Lecithin*, *nicotinic acid*

and cholin^{3,10} are inert in similar experiments. Methionine evidently is the key amino-acid; it was suggested that it acts through some enzyme system.

Table 3 shows that 4.8 gm. methionine given as indicated insures complete protection against a double lethal chloroform anesthesia (40 minutes). We note no icterus, no fall in fibrinogen and no clinical intoxication. When the same dog is given only 20 minutes' chloroform there is a fatal poisoning in spite of the six amino-acids listed in Table 3 given in doses of 1 gm. each 21 hours and again 4 hours before the chloroform anesthesia. The liver shows the characteristic hyaline necrosis, there is icterus and a subnormal fibrinogen.

Utilization of plasma protein may be regarded as established by experiments with plasma protein given by vein to maintain nitrogen equilibrium for weeks in a protein fasting dog. Proteins appear in various organs (liver) and tissues (muscle),¹ but probably in the form of the specific cell protein. The mechanism of this reaction has been studied by Howland and Hawkins.²⁰ In phlorizinized dogs the injected (vein) plasma protein does not increase the urinary nitrogen and dextrose, as is found when the same plasma protein is fed under identical circumstances. The injected plasma protein promptly disappears within 24 hours and must be in the cells and tissues. It appears that the plasma protein is metabolized without increase in the amino-acids in the body fluids—that is, without cleavage to the amino-acid level. This suggests a modification of the plasma protein entering the cells by means of a cleavage into large aggregates and reassembly into the normal cell proteins. This procedure can supply all the immediate protein requirements of the body.

Schoenheimer and Rittenberg^{31,35} have added important information about intermediary metabolism which indicates that the liver protein and plasma protein are most active in the turnover of the heavy isotope containing amino-acids. Their experiments are in accord with a balanced system of body protein in which plasma proteins and liver proteins are most active.

Evidence cited above indicates that protein molecules can *emerge* from a cell and also *enter* a cell readily—a dynamic equilibrium between cell and plasma protein. This forces us to consider how these large protein molecules pass in and out through cell surface membranes. We may focus our attention on the *liver* cell as these cells can produce proteins (*e. g.*, fibrinogen) and can take in proteins from the plasma.¹ These liver cells are also peculiar because they contain canaliculi—tiny passages *within the liver cell protoplasm* which communicate with the bile capillaries and have to do with the outflow of bile salts and bile pigments.

Surface membranes as described by Krogh²² are ill-defined and closely bound up with the cell protoplasm of which they form the

boundary zone. Such membranes restrict the free movement of molecules and particles but are not concerned with any energy requiring *transport* of substances across its thickness.

Surface membranes are generally believed to be a mixture of lipids, proteins and perhaps other substances. They may be arranged as a *mosaic* in which the proteins and other substances are distributed in a regular or haphazard manner (Rideal³²). The arrangement may be in *layers* of protein and lipid material giving a lipid-protein surface to the plasma membrane designated in its simplest form as a bimolecular layer of lipid molecules between two layers of protein molecules (Harvey and Danielli¹⁵).

Physiologists have much to say about the behavior of electrolytes and small molecules as related to surface membrane passage, but in general maintain a discreet silence about membrane passage of protein molecules. Perhaps this is evidence of wisdom, but our interest in the ebb and flow of proteins between the cell and blood plasma has forced us to speculate about it. If the surface membrane of the liver cells is a mixture of protein and lipid, these proteins must be intimately related to other cell proteins *including ferments*. We can see no reason why these ferments may not be able to modify the surface membrane so that cell proteins needed by the body can emerge as they are formed rapidly within the cell. Incoming proteins from the plasma protein pool could pass through the surface membrane in the same fashion, preceded by adsorption on the surface.

The argument that these proteins are broken down to amino-acids to permit surface membrane passage does not stand analysis—the *outgoing* protein, if broken down at the surface would appear as amino-acids in the blood plasma and be treated as such, there being no evidence that proteins are synthesized outside of the cell proper. If the *incoming* proteins were broken down to amino-acids at the surface, we would expect some escape of the amino-acids into the blood plasma and this reaction would be detectable in careful study of nitrogen metabolism.²⁰ When a dog is kept in nitrogen and weight equilibrium for weeks by feeding sugar and fat by mouth and giving plasma by vein, there is evidence⁵⁶ that this plasma protein is used *without wastage* of nitrogen, in contrast to the findings when protein is fed. We have assumed from this and other evidence that the introduced plasma protein passed into body cells needing protein and within the cell was modified by cleavage or other means due to ferment activity to furnish the particular protein needed (liver, muscle and so forth).

Stimuli which are responsible for the *increase* in any given *blood protein* should be mentioned, even if little can be said other than that our ignorance is almost complete. It is believed that anoxemia is a stimulus to hemoglobin production but it is probable that other

factors enter into the reaction.^{33b} The stimuli responsible for plasma protein production certainly are variable. Who will even guess at the nature of the stimulus relating to the production of *fibrinogen* by the liver? Fibrinogen is a labile protein which may show wide fluctuations within the space of a day or so, related to liver injury, tissue injury, hemorrhage, and many other factors.^{7,23} Fibrinogen normally makes up but 10% of the plasma globulins, so that one cannot say that any significant change in osmotic pressure is responsible for or related to these changes in fibrinogen. We may say a nice balance between use and production of fibrinogen is maintained at about 0.3 gm. per 100 cc. in the plasma of the dog, but the stimuli which change this level are various and their mode of operation quite obscure. It is probable that hypoproteinemia in some obscure manner does accelerate the production of new plasma albumin and globulin²⁵ but the fact that proteins can pass to and fro easily between cells and plasma makes the interpretation of experiments difficult.

DYNAMIC EQUILIBRIUM OF BODY PROTEINS

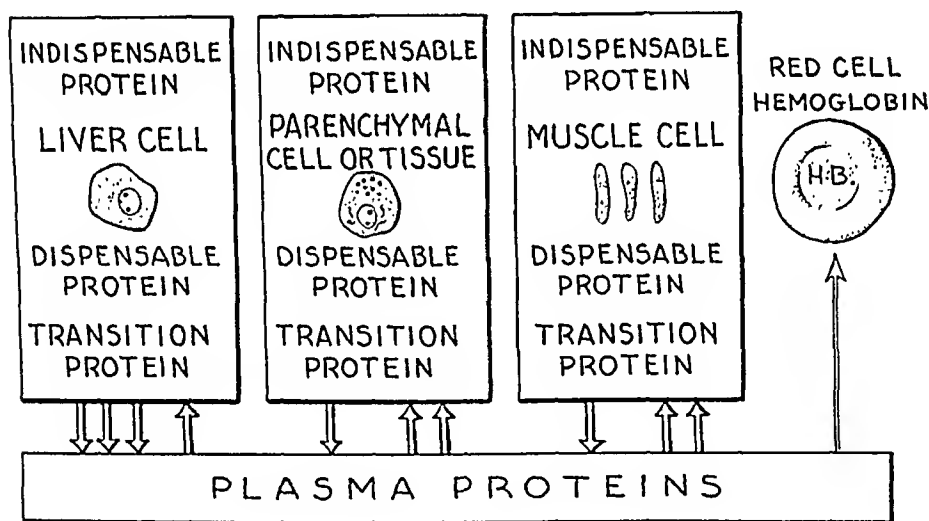


FIG. 1.

Figure 1 is an attempt to picture certain features of protein metabolism as we see it. We believe that the liver is strategically situated and of sufficient size to take on most of the work of *protein synthesis*. Many plasma proteins emerge from the liver cells and can be used in the body to supply all or most of its protein requirements. Figure 1 indicates by arrows that the liver cell can store protein and that it can give out stored protein or fabricated protein. The protein on its way out or in is simply designated as *transition protein* which by cleavage and reassembly (ferments) is on its way to cell

protein or to plasma protein. Much cell protein cannot be removed and is called indispensable. Parenchyma or tissue cells, including muscle cells, as indicated by arrows can act to store proteins or to use proteins or to release stores and perhaps to fabricate protein in a small way. We believe the plasma protein can contribute to the manufacture of red cell hemoglobin but there is no evidence of an outflow of protein from these red cells short of cell breakdown.

One may choose to look at the *liver cell* as a boiling cauldron into which go amino-acids and proteins, lipids, carbohydrates, salts, accessories and water. In this cauldron the boiling includes ferment action and leaves nothing sacred—amino-acids are broken up and reassembled from the mangled remnants, radicles are pulled out and others replaced in large aggregates (including proteins). Ultimately and frequently in a short span there emerges a beautiful thing, a protein—fibrinogen or prothrombin for example—and who will care to write the work specifications for its manufacture?

Conclusion. We may now attempt to formulate briefly our understanding of plasma protein metabolism. Food proteins yield the amino-acids absorbed from the intestinal tract and the amino acids are synthesized in the liver cells (and elsewhere) into plasma proteins. These plasma proteins (and amino-acids) supply the protein requirements of the body cells. Normally there is a considerable reserve of plasma protein forming material (1 to 5 times the circulating mass) which reserve may be reduced by fasting, low protein diet or plasma depletion. This depletion of protein reserves lowers the body resistance to infection and intoxication. These body protein stores, protein production and protein wear and tear are in a nicely balanced or *steady state*—a dynamic equilibrium. These proteins can pass readily from plasma into cells and the reverse, without loss of nitrogen. The passage of proteins through cell surfaces is discussed and also the obvious recasting of cell protein into plasma protein and the reverse.

Hemoglobin in its production may draw on the plasma protein but hemoglobin stands apart in the protein economy and does not contribute freely to the protein pool. On the other hand, the body guards jealously the fabrication of hemoglobin and given a real need for both plasma protein and hemoglobin the protein flow favors hemoglobin, which under these circumstances always is produced in more abundance than the plasma protein.

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DIABETES MELLITUS AND TUBERCULOSIS.*

By MORTON F. MARK, M.D.,

ASSISTANT VISITING PHYSICIAN, SEA VIEW HOSPITAL,

HERMAN O. MOSENTHAL, M.D.,

PROFESSOR OF CLINICAL MEDICINE, COLUMBIA UNIVERSITY; CONSULTING PHYSICIAN,
SEA VIEW HOSPITAL,

AND

FLORA LIU, M.D.,

RESIDENT PHYSICIAN, SEA VIEW HOSPITAL,
NEW YORK CITY, N. Y.

(From the Metabolism Service of Sea View Hospital.)

THE frequent combination of tuberculosis and diabetes has made the study of the associated diseases an important subject for many years. The concurrence of tuberculosis and diabetes formerly was often found in 42% to 50% of diabetics (Curschmann⁹). Improved diabetes therapy, especially the introduction of insulin, resulted, according to King,^{20b} in a drop of tuberculosis incidence in diabetics in the United States from 12% prior to 1922, when insulin became available, to 2.5% since that time. Although there is a great deal of satisfaction in this accomplishment, yet much remains to be done, since it is known that tuberculosis develops almost three times as frequently among diabetics as in the general population (Root,^{30a} Banyai²) and this fact justifies a review of the extensive material, 349 cases of combined tuberculosis and diabetes, treated on the metabolism service of Sea View Hospital from January 1, 1934, to December 1, 1939.

Age at Onset of Tuberculosis. Tuberculosis appeared after the age of 40 in 258 (73.9%) of the 349 diabetics (Table 1). Wiener and Kavee⁴¹ found this in 81.2%, and Meyers and McKean²⁴ in 60% of their patients. This peak of onset after the age of 40 is in contrast to that for non-diabetics in whom it occurs at a much earlier age. The age distribution of tuberculosis in diabetic patients thus coincides with the age distribution of diabetes rather than that of tuberculosis.

Predisposition of Diabetics to Tuberculosis. The onset of diabetes usually precedes that of tuberculosis (Kennedy,¹⁹ Wiener and Kavee,⁴¹ Meyers and McKean,²⁴ Ralli and Steinberg,²⁹ Himsworth,¹⁷ Root and Bloor³¹). Of the 349 cases in the present study (Table 2), the diabetes was the primary disease in 208 (59.6%) and the tuberculosis in 81 (23.2%). In 60 cases (17.2%) both conditions were discovered simultaneously. If only those cases are considered in which the date of onset of each disease was known, then the diabetes was the primary illness in 72%.

The fact that diabetes usually precedes the advent of tuberculosis suggests that diabetes predisposes to tuberculosis. There is con-

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siderable evidence to support this view. As already pointed out, according to the analyses of Root^{30a} and of Banyai,² tuberculosis is about three times as frequent in diabetics as in non-diabetics. Root and Bloor³¹ noted that in their diabetic patients whose diabetes began before the age of 20, tuberculosis occurred twelve times as frequently as among all pupils in Massachusetts grade and high schools. In another study of his diabetic children, Root^{30a} noted an increasing incidence of tuberculosis on repeated examination, indicating that the longer the patient has diabetes, the greater is the probability that he will develop tuberculosis.

TABLE 1.—AGE AT ONSET OF TUBERCULOSIS IN 349 CASES OF DIABETES AND TUBERCULOSIS.

Age.	Cases.			Per cent.
	Male.	Female.	Total.	
Under 20	5	6	11	3.2
20 to 29	20	13	33	9.5
30 to 39	28	19	47	13.5
40 to 49	66	37	103	29.5
50 to 59	47	54	101	28.8
60 and over	22	32	54	15.5
Total	188	161	349	

Tuberculosis in diabetics appeared after the age of 40 in 258 of the 349 cases (73.9%). The peak of onset in non-diabetics is considerably earlier.

TABLE 2.—RELATION OF ONSET OF TUBERCULOSIS AND DIABETES (349 CASES). DIABETES USUALLY THE PRIMARY DISEASE.

	No. of cases.	%.	Primary diagnosis, %.
Diabetes, primary	208	(59.6)	72
Tuberculosis, primary	81	(23.2)	28
Simultaneous discovery	60	(17.2)	

Probably there has been neglect when the discovery of the two conditions is simultaneous. If we consider only the cases in which there is a primary diagnosis, it is found that diabetes is the primary disease in 72%.

There is also experimental evidence to suggest that diabetes renders the animal more susceptible to tuberculosis. Steinbach, Klein and Deskowitz³⁵ were able to produce tuberculosis by intraperitoneal inoculation in 6 out of 7 dogs rendered diabetic by pancreatectomy, whereas 8 control animals were negative for tuberculosis after similar injections. The dog is normally very resistant to tuberculous infection.

The available data indicate that it is uncontrolled diabetes, rather than diabetes *per se*, that is responsible for the greater susceptibility to tuberculosis (Root,^{30b} Root^{30c} Himsworth¹⁷). Twenty to 50% of Root's cases had had acidosis or coma prior to the appearance of tuberculosis, and Himsworth observed that in all of his patients, there had been no, or inadequate, treatment of the diabetes. Similar conclusions were reached in the investigation of our cases. On the other hand, in a series of well-regulated diabetics, Himsworth

worth¹⁷ observed an incidence of tuberculosis of only 0.7%, which is no higher than that found in the general population. Many observations have shown that the controlled diabetic approaches the non-diabetic in his resistance to infection (Moen and Reismann,²⁵ Mosenthal,²⁶ Bayne-Jones³) and it would seem that the same should hold true in regard to withstanding an invasion by the tubercle bacillus.

Severity of the Diabetes in Patients With Diabetes and Tuberculosis. On theoretical grounds, one would expect that severe diabetics would be more susceptible to tuberculosis than mild diabetics, since the severe diabetic is more likely to pass through periods in which the diabetes is not adequately controlled. There is some difference of opinion on this point. Root^{30c} found that the average insulin requirement of his tuberculous diabetics was not appreciably higher than that of the patients with uncomplicated diabetes. On the other hand, Himsworth¹⁷ states that tuberculosis is a complication of severe, rather than mild, diabetes. Our observations agree with those of Himsworth. The cases have been grouped according to the severity of the diabetes in Table 3. Since these patients were all on a fairly uniform diet it was reasonable to classify them on the basis of their insulin requirement. Patients who received less than 20 units of insulin a day were considered mild, those requiring 20 to 40 units moderately severe, and those who needed more than 40 units were classified as severe. According to these criteria, 32.6% of the patients were mild diabetics, 24.4% were moderately severe and 43% severe. It is evident that the predominant number were in the severe group.

TABLE 3.—SEVERITY OF DIABETES IN CASES OF COMBINED TUBERCULOSIS AND DIABETES.

	No. of cases.	%.
Mild:		
Less than 20 units insulin	114	32.6
Moderately severe:		
20 to 40 units insulin	85	24.4
Severe:		
Over 40 units insulin	150	43.0

The predominant number of tuberculous diabetics have severe diabetes. This is in contrast to patients with uncomplicated diabetes.

Extent of Tuberculosis on Admission. In Table 4, the 349 cases of diabetes and tuberculosis have been analyzed from the point of view of the type of tuberculosis on admission and the course of the tuberculous disease during the hospital stay. The most striking feature is the large number of patients with far-advanced disease when first observed and the very small percentage of cases with minimal involvement. Only 11.4% of the 349 cases had minimal lesions at the time of admission. In 30.6% the tuberculosis was moderately advanced, and in 58% it was far advanced. Similar observations on the late diagnosis of tuberculosis in diabetic patients

have been made by Ralli and Steinberg,²⁹ Meyers and McKean,²⁴ Banyai,² Root.^{30b}

TABLE 4.—EXTENT OF TUBERCULOSIS ON ADMISSION AND THE RESULTS OF TREATMENT.

Status of tuberculosis at time patients left hospital.	Type of tuberculosis on admission.			Totals.
	Minimal.	Mod. advanced.	Far advanced.	
Cases:				
Number	40	107	202	349
Per cent	11.4	30.6	58.0	
Apparently arrested cases:				
Number	16	37	19	72
Per cent	40.0	34.6	9.4	20.6
Arrested cases:				
Number	1	2	0	3
Per cent	2.5	1.9	0	0.9
Stationary cases:				
Number	12	23	21	56
Per cent	30.0	21.5	10.4	16.0
Progressive cases:				
Number	8	21	74	103
Per cent	20.0	19.6	36.6	29.5
Death cases:				
Number	3	24	88	115
Per cent	7.5	22.4	43.6	33.0

Only 11.4% of the patients had minimal tuberculosis at the first observation, whereas 30.6% were moderately advanced, and 58% were far advanced. The diagnosis of tuberculosis in diabetics entering Sea View Hospital is made later than it should be. The prognosis depends upon the extent of the tuberculosis when first discovered. An arrest of the disease was obtained in 42.5% of the minimal cases and in only 9.4% of the far-advanced cases.

Several reasons may be given for the delayed recognition of a disease that often proves fatal:

1. Untreated or poorly managed diabetics are not only more susceptible to tuberculosis than normal individuals or well-controlled diabetics, but also, the tuberculosis progresses in them with exceeding rapidity.

2. The early symptoms of tuberculosis simulate those of diabetes so that the physician is likely to attribute such symptoms as loss of weight, fatigability, and so on, to the diabetes.

3. The frequent absence of physical findings in diabetic tuberculous patients, so that the disease is often not recognized until the advanced stage has been reached. The lack of physical signs in many cases of minimal and moderately advanced tuberculosis in non-diabetics as well as in diabetics is now well recognized.

Results of Treatment. Of the 40 cases with minimal tuberculosis (Table 4), on admission, 17 (42.5%) were apparently arrested or arrested at the expiration of the hospital stay, while of the moderately advanced cases, 35.5% were either apparently arrested or arrested. In the far-advanced group, only 19 of 202 patients (9.4%) could be classified as apparently arrested cases. An analysis of the deaths showed that only 7.3% of the minimal disease cases died, whereas 22.4% of the moderately advanced and 43.6% of the

far-advanced cases terminated fatally. These results demonstrate strikingly that the prognosis of tuberculosis in diabetic individuals depends to a great extent upon the stage of the tuberculosis at which therapy is instituted. In this respect tuberculosis in the diabetic and in the non-diabetic are alike.

Treatment of the Diabetes. The most important factor for the successful control of tuberculosis in diabetics is the effective management of the diabetes.

Diet: The caloric intake should be regulated so that the body weight is slightly above the calculated normal. Obesity is undesirable both for the diabetes and for the tuberculosis. Most tuberculosis patients will gain weight on a diet of 2000 calories, more than 2500 calories are rarely required. An adequate vitamin and mineral intake is, of course, essential.

It has been our practice to prescribe a diet with a carbohydrate value of 150 to 200 gm.—that is a moderately high carbohydrate diet. The beneficial effect of a high fat, low carbohydrate diet on the course of the tuberculosis, claimed by Meyers and McKean,²⁴ has not been substantiated by other evidence (Keaton,¹⁸ King,^{20a} Freilich and Coe¹⁵), and this diet has the disadvantage of being less palatable than a diet of higher carbohydrate value. It is also our opinion that, because of the increased protein destruction that occurs in tuberculous individuals, as a result of fever and toxemia, a liberal protein intake is advisable. As a rule, most patients do well with about 90 gm. of protein per day. Fat is added to make up the total caloric value.

Insulin should be used whenever adequate nutrition and a sugar-free urine cannot be maintained on diet alone. The pulmonary focal reactions previously reported as resulting from insulin (Wassmund,³⁸ Fishberg¹³) were probably due to protein impurities in the insulin preparations (Allen,¹ King^{20a}). In the present series, insulin was required in 278 out of the 349 cases. Seventy-one patients were regulated by diet alone; in 43 cases, less than 20 units of insulin were required; in 85, between 20 and 40 units; and in 150, over 40 units of insulin per day were necessary. Regular insulin was used exclusively in 131 cases while 147 cases protamine zinc insulin alone or protamine zinc and regular insulin were given. Since the introduction of protamine zinc insulin in 1936, we have resorted to this preparation in almost every case.

The value of protamine zinc insulin, in the treatment of diabetes complicated by tuberculosis, has been mentioned in previous studies (Mark, Sackey and Mosenthal,²² Mosenthal and Mark^{27a}). It has been stressed that more adequate control of glycosuria and fewer hypoglycemic reactions result from the use of protamine zinc insulin than from regular insulin. This opinion has been substantiated by others (Elwood,¹¹ Root and Bloor³¹).

Of greater interest is the favorable effect protamine zinc insulin

might have on the course of the tuberculous disease (Mosenthal and Mark^{27b}). One hundred and thirty-one patients were treated with regular insulin and 147 with protamine zinc insulin (Table 5). A number of patients died or left the hospital within a few months after admission so that in these cases too short a time had elapsed to permit an interpretation of the influence on the tuberculous disease of either type of insulin. A separate analysis was, therefore, made of those patients who had been receiving either preparation for 6 months or more. These results are also recorded in Table 5. Eighty-three patients who had been given protamine zinc insulin for more than 6 months are compared with 63 who were regulated with regular insulin for a similar period. In 32.5% of the protamine zinc insulin cases, the tuberculosis became arrested or apparently arrested as compared with 21.9% for the regular insulin group. Of the regular insulin group, 43.7% died as compared with 8.4% for the patients taking protamine zinc insulin. It is believed that the protamine zinc insulin was responsible for the more favorable results since the extent of the tuberculosis on admission and the type of therapy were essentially the same for both groups.

TABLE 5.—COMPARISON OF CLINICAL COURSE OF TUBERCULOSIS IN DIABETICS TREATED WITH PROTAMINE ZINC INSULIN OR WITH REGULAR INSULIN.

Status of tuberculosis at end of hospital stay.	Total cases.				Cases receiving insulin for 6 months or more.			
	Insulin.				Insulin.			
	Regular. No.	%	Protamine zinc. No.	%	Regular. No.	%	Protamine zinc. No.	%
Arrested	0	0	5	3.4	0	0	5	6.0
Apparently arrested	17	13.0	28	19.0	14	21.9	22	26.5
Regressive	0	0	9	6.1	0	0	9	10.9
Stationary	12	9.1	33	22.5	3	4.7	23	27.7
Progressive	44	33.6	45	30.6	19	29.7	17	20.5
Died	58	44.3	27	18.4	28	43.7	7	8.4
Total	131		147		64		83	

The course of the tuberculosis is more favorable when the diabetes is treated with protamine zinc insulin than with regular insulin.

The most probable explanation for the favorable influence of protamine zinc insulin on the course of the tuberculosis in tuberculous diabetes is that it provides a continuous control of the diabetic process and consequently a better state of nutrition. This view is supported by the work of Wilder.⁴² He showed that with the customary use of regular insulin, intervals may occur during the 24 hours when a negative nitrogen balance and protein destruction prevail. On the other hand, with protamine zinc insulin, no periodic intervals of nitrogen loss were encountered, even when a moderate glycosuria was permitted. Tolstoi and Weber,³⁷ in a careful observation on 2 severe diabetics receiving protamine zinc insulin, found that these

patients remained in nitrogen balance in spite of the fact that a marked glycosuria was permitted.

Effect of the Course of the Tuberculosis on the Diabetes. Lundberg²¹ has stressed the beneficial influence of tuberculosis on diabetes. He discovered that in some cases as the tuberculosis progressed, the carbohydrate tolerance improved, and also that many of his patients on insulin treatment developed unexpected reactions. He postulated the elaboration in tuberculous tissue, of an insulin-like substance which he called para-insulin. This view has not been supported by many clinicians who have had the opportunity to study the combined disease (Rosenberg and Wolf,³² Curschmann,⁹ Fitz,¹⁴ King^{20a}).

In our studies, we have also observed occasional instances in which rapid progression of the tuberculosis was associated with a diminished insulin requirement. We are inclined to agree with Allen¹ that the improved tolerance in these cases could be attributed to the poor appetite, tissue destruction and consequent undernutrition, associated with rapidly progressive tuberculosis. However, some cases, as Lundberg admits, require greater amounts of insulin when the tuberculosis progresses.

TABLE 6.—EFFECT OF TUBERCULOSIS ON DIABETES.

Course of tuberculosis.	Cases.		Severity of diabetes.					
			Increased cases.		Decreased cases.		Unchanged cases.	
	No.	%.	No.	%.	No.	%.	No.	%.
Progressive . . .	218	62.5	64	29.3	63	29.0	91	41.7
Improved . . .	75	21.5	22	29.3	22	29.3	31	41.4
Stationary . . .	56	16.0	16	28.6	11	19.6	29	51.8
Total	349		102	29.2	96	27.5	151	43.3

The course of the tuberculosis does not seem to have any constant effect on the severity of the diabetes. The favorable effect on the severity of the diabetes observed in some cases of progressive tuberculosis is probably due to the associated undernutrition and diminished food intake.

In Table 6, an attempt has been made to determine the effect of a change in the tuberculous lesion on the severity of the diabetes.

The severity of the diabetes was determined by comparing the insulin requirement shortly after admission to the hospital with that at the time of discharge or death. In 29.3% of the 218 cases in which the tuberculosis progressed, the severity of the diabetes increased. In 29% it diminished and in 41% it remained unchanged. Similar results were observed in groups of patients in whom the tuberculosis improved. From this analysis it appears that the course of the tuberculous disease has no constant effect on the severity of the diabetes.

Type of Treatment for the Tuberculosis. The same type of treatment was accorded the diabetics as the non-diabetics received since it was felt that the controlled diabetic could undergo the same

procedures as the non-diabetic. However, the effects of a previously uncontrolled diabetes, notably arteriosclerosis and coronary disease, did influence the final decision, and because of these complications as well as the more advanced age of diabetic tuberculous patients, only a small number were subjected to the more radical surgical procedures such as thoracoplasty. In Table 7, the 349 cases are grouped according to the type of therapy used for the tuberculous disease.

TABLE 7.—TYPE OF TUBERCULOSIS THERAPY IN 349 TUBERCULOUS DIABETICS.

Type of therapy.	No. of cases.	%.
Conservative	205	58.7
Pneumothorax	119	34.1
Intrapleural pneumonolysis	20	5.1
Thoracoplasty	5	1.5
Total	349	

Conservative Therapy. Of the 349 cases, 205 (58.7%) were treated conservatively. This group included some patients who had incipient lesions with negative sputum, but the majority were either too far advanced for more radical procedures or had some other condition such as cardiac disease that was considered a contraindication to surgical therapy. The results in this group of cases are recorded in Table 8.

TABLE 8.—RESULTS OF CONSERVATIVE TUBERCULOSIS TREATMENT IN TUBERCULOUS DIABETICS.

Result.	No. of cases.	%.
Arrested	1	0.5
Apparently arrested	29	14.1
Stationary	35	17.4
Progressive	67	32.7
Death	73	35.6
Total	205	

Unfortunately, statistics for the results in non-diabetic tuberculous patients treated conservatively at Sea View Hospital are not available so that a comparison cannot be made. To compare these results with those reported from other institutions might be misleading since the selection of cases for conservative or for surgical therapy varies considerably. It is, therefore, impossible to decide whether tuberculous in diabetics responds as well to conservative therapy as it does in non-diabetics. However, it is evident that the view expressed by earlier authors (Sossman and Steidl,³⁴ Fitz,¹⁴ Fishberg¹³) that tuberculous in diabetics is always progressive is not borne out. We have frequently observed patients in whom even a far-advanced lesion has healed by fibrosis, and it is our impression that with adequate and careful control of the diabetes, the prognosis of the tuberculous approaches that in the non-diabetic. This view is now generally accepted (Banyai,² Root,³⁰ Wessler

and Hennell⁴⁰). It should, however, be pointed out that this is only an impression. So far, no comparison has been made between large groups of diabetic and non-diabetic tuberculous patients.

Pneumothorax. Out of a total of 349 cases of diabetes and tuberculosis, pneumothorax therapy was performed in 139. In 20 of these, intrapleural pneumonolysis was done at some time during the course of therapy in an attempt to convert an ineffective pneumothorax into an effective one. This group has been the subject of a separate study and will be referred to subsequently. For the present, an analysis of 119 patients who received pneumothorax therapy alone will be made. This group includes 13 patients in whom thoracoscopy was performed, but no attempt at the severing of adhesions was made.

Of the 119 pneumothorax cases, 63 were male and 56 female. Seven patients were subjected to bilateral pneumothorax and 112 to unilateral pneumothorax. The age distribution is recorded in Table 9. The majority of the patients were in the age group above 40. It is noteworthy that 37 patients were more than 50 years of age. In our experience elderly individuals tolerate pneumothorax perfectly well, but age is a factor to be considered in the expected results from pneumothorax treatment. Bendove,⁵ in his study of pneumothorax results in non-diabetic tuberculous patients at Sea View Hospital, found that the results were considerably better in patients under 40 years than in those above this age. It is evident, therefore, that the results in diabetic patients who are mostly over 40 years are not strictly comparable with non-diabetics, the majority of which are below this age.

TABLE 9.—AGE DISTRIBUTION OF CASES SUBJECTED TO PNEUMOTHORAX.

Age.	No. of cases.
Under 20	2
20 to 29	17
30 to 39	21
40 to 49	42
50 to 59	30
60 and over	7
Total	119

Bendove⁴ and his coworkers have pointed out that sputum conversion is the most reliable index of the effectiveness of pneumothorax therapy. The analysis of our results was therefore made on the basis of whether this therapy was successful in converting the sputum from positive to negative. In the sputum-negative group are included all cases in which the sputum remained persistently negative on plain smears and concentrates for a period of at least 6 months. The improved group consists of those patients in whom the sputum was negative for a period of less than 6 months. The results are recorded in Table 10. Of the 119 cases, 29 (24.4%) can

be classified as sputum-negative and 19 (16%) of the total as improved—that is, had a negative sputum for less than 6 months.

TABLE 10.—RESULTS OF PNEUMOTHORAX IN CASES OF DIABETES AND TUBERCULOSIS.

Total cases.	Sputum negative.		Improved.		Sputum positive.	
	Cases.		Cases.		Cases.	
	No.	%.	No.	%.	No.	%.
119	29	24.4	19	16.0	71	59.6

The studies of Bendove⁴ and his coworkers were also carried out at Sea View Hospital and hence furnish a basis for measuring the effectiveness of pneumothorax in cases of diabetes complicated by tuberculosis. They found that 546 (41%) of 1320 patients receiving pneumothorax therapy became sputum-negative. Even if we allow for the age factors, since most of the diabetics were over 40 years, there is still a significantly lower percentage of sputum-negative cases among the diabetics. The reason that diabetics do not respond as well to pneumothorax therapy as non-diabetics is not apparent. *Complications of Pneumothorax.* The principal complications resulting from pneumothorax are hydropneumothorax, tuberculous empyema, mixed infection empyema, bronchopleural fistula, spontaneous pneumothorax and air embolism. The incidence of these complications is recorded in Table 11. Hydropneumothorax was observed in 38 (33.3%) of the cases. For non-diabetics, Matson²³ reported the occurrence of hydrothorax in 17.3% of his pneumothorax cases, while Hayes¹⁶ observed it in 61%, Burrel⁷ in 41.4%, Weisman³⁹ in 84%, and Dumarest and Brette¹⁰ in 70%. The incidence of hydrothorax in diabetics is, therefore, no greater than that reported for non-diabetic individuals.

TABLE 11.—COMPLICATIONS OF PNEUMOTHORAX THERAPY IN 114 TUBERCULOUS DIABETICS.

Complication.	No. of cases.	
	No.	%.
No complications	45	39.5
Hydrothorax	38	33.3
Tuberculous empyema	17	14.9
Mixed infection empyema	1	0.9
Bronchopleural fistula	4	3.5
Spontaneous pneumothorax	7	6.1
Air embolism	1	0.9
Hemothorax	1	0.9

Tuberculous empyema was observed in 17 patients and mixed infection empyema in 1. Empyema was, therefore, a complication in 15.7% of the cases. For non-diabetic patients, Hayes¹⁶ reported this serious complication in 21% of his cases, Burrel⁷ in 11.6%, Dumarest and Brette¹⁰ in 16%, Naveau²⁸ in 20% and Matson²³ in 12%. It would thus seem that tuberculous empyema is a complication no more frequent in tuberculous diabetics than in non-diabetics.

Bronchopleural fistula was recognized clinically in 4 cases. Three of these were associated with tuberculous empyema and 1 with a mixed infection empyema. Spontaneous pneumothorax superimposed on therapeutic pneumothorax occurred in 7 cases (6.1%). This incidence is somewhat higher than that reported by Matson,²³ who observed this complication in only 3% of his non-diabetic patients. Air embolism and spontaneous hemothorax each occurred in 1 instance.

From this analysis we can conclude that the complications of pneumothorax in tuberculous diabetics are not appreciably higher than in non-diabetics, but that the results of this procedure are less favorable in diabetic individuals. This observation should not discourage the use of pneumothorax in these patients since the results are better than could be expected from conservative therapy.

Intrapleural Pneumonolysis. The results of intrapleural pneumonolysis in tuberculous diabetics have been the subject of a separate study carried out by Drs. Harry Epstein and Flora Liu.¹² Their findings are freely quoted here. The procedure was attempted in 33 of the 139 tuberculous diabetics who were subjects of pneumothorax therapy. Of the 33 cases, adhesions could be severed in only 20. In 7 of the 33 cases, the operation was performed in two stages, and in one in three stages, making a total of 42 operations. The operation resulted in closure of the cavity in 13 of 20 patients. These results are comparable to those reported by Stemmerman and Tcherkoff³⁶ on non-diabetic patients at Sea View Hospital and to those of Brissaud⁶ and of Smith³³ from other institutions. However, the diabetic group is too small to be of great statistical significance.

Complications of intrapleural pneumonolysis seem to be more frequent in diabetic patients. Empyema, for example, followed the procedure in 27.2% of the cases—an incidence which is considerably higher than 5.8% to 9% reported for non-diabetics (Stemmerman and Tcherkoff,³⁶ Coryllos,⁸ Smith³³).

Thoracoplasty was performed in 5 patients. In 1 of these a one-stage procedure was carried out and in the remaining 4, two stages. Three of the patients died. In 2 of these death was directly attributable to the operative procedure. One died after a first-stage operation and the other following the second stage. The third death resulted from insulin resistance and diabetic coma, the patient dying 26 months after the operative procedure. In this case the tuberculosis continued to progress after operation. In 1 instance the tuberculosis was arrested and in another apparently arrested as a result of thoracoplasty.

The number of our cases subjected to thoracoplasty is obviously too small to permit any conclusions as to the results of this procedure in tuberculous diabetics. All that can be said is that these patients can be subjected to thoracoplasty and if the diabetes is well controlled, they do not develop unusual complications. It was inter-

esting to note that in none of the cases did serious postoperative infections develop. Of the 2 postoperative deaths, 1 died of shock and the other of an hemoptysis—complications that cannot be attributed to the diabetes.

Effect of Operative Procedures on the Diabetes. Pneumothorax had no effect on the control of diabetes and consequently no special measures for diabetic care were necessary. This was true for both the initial procedure and for subsequent refills. A fair number of patients subjected to intrapleural pneumonolysis or thoracoplasty did manifest a moderate glycosuria postoperatively and in a few mild ketonuria was present. In all of these, the diabetes was brought under control within 2 or 3 days; the usual measures taken in the control of diabetes subjected to surgical procedures were employed. It was preferable to have the operation performed early in the morning. Patients who were previously taking regular insulin continued to take it, but for the first day or two the insulin was administered at 4-hour intervals in doses depending upon the urinary findings during these periods. Those who had been taking protamine zinc insulin prior to operation were given the same dose of protamine zinc immediately after the operation. Regular insulin was added as required at 4-hour intervals.

Summary and Conclusions. An analysis is presented of 349 cases of diabetes and tuberculosis (188 males and 161 females) observed at Sea View Hospital during the years 1934 to 1939, inclusive. Diabetes usually precedes the tuberculosis.

The age of onset of the tuberculosis in diabetics (73.9% after 40 years of age in this series) is much older than in non-diabetics. Poorly controlled diabetes predisposes to tuberculosis and causes rapid progression of the disease, whereas effectively treated diabetics are no more subject to tuberculosis than normal persons, and in well-controlled diabetics, the results of treatment compare favorably with those obtained in non-diabetic tuberculous patients.

The clinical course of the tuberculosis was very much better when the diabetes was managed with protamine zinc insulin than when regular or crystalline insulin was employed.

The tuberculosis was treated conservatively in 205 of the 349 cases (58.7%). Of the remainder, 139 patients received pneumothorax and in 20 of these, intrapleural pneumonolysis was done; 5 patients were subjected to thoracoplasty.

Pneumothorax in tuberculous diabetics was not as successful as in non-diabetics, although complications of pneumothorax were no greater in diabetics than in non-diabetics.

Complications of intrapleural pneumonolysis, particularly empyema, were more frequent in diabetics than in non-diabetics.

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THE HISTOPATHOLOGIC PROGNOSIS OF SALIVARY GLAND MIXED TUMORS.

BY JOSEPH MCFARLAND, M.D., Sc.D.,

EMERITUS PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF PENNSYLVANIA; PROFESSOR OF GENERAL PATHOLOGY IN THE TEMPLE UNIVERSITY DENTAL SCHOOL, PHILADELPHIA, PA.

(From the Laboratory of Pathology, School of Medicine, University of Pennsylvania.)

As indicated in previous publications^{1a-f} upon these tumors, my interest was directed to their peculiar structure and more peculiar clinical behavior some 20 years ago. I found them somewhat rare, very diversified in structure, and divisible into numerous subgroups, but not enough of them came into my hands to satisfy my requirements for a careful analytical study. In order to obtain an adequate number, I searched the records of the leading hospitals in and about Philadelphia, examined their microscopic sections and copied their case histories, inquiring from year to year what additions they may have had to add to my collection. I also maintained through inquiry, correspondence and visitation a fairly efficient

"follow-up." For the universal courtesy and coöperation shown me, I now desire to express my sincere thanks to each of the friends who gave me of his time and material.

The number of cases thus brought together has now reached 421. But in the following tabulations and computations, that total never appears, as some of the cases of which I have studied the microscopic sections were unaccompanied by any data, and sometimes I found data upon cases for which microscopic sections were no longer available.

As my chief interest centered about the so-called "mixed tumors," at first I asked for no other varieties. But it soon became evident that other captions would have to be called upon, as the different theories for accounting for the origin of the tumors, their various appearances and the personal opinions of the pathologists by whom they were examined, led to confusion of nomenclature, so that similar tumors might appear under such different names as mixed tumors, endotheliomas, adenocarcinomas, myxochondromas, carcinomas, enclavomas, branchiomas and adenomas. A few were even designated sarcomas. It was from all these groups that my cases were finally selected after careful examination of the microscopic slides and consideration of the protocols, when available. But notwithstanding all my care, I find included in my material at least 21 cases that do not seem to be mixed tumors. Whether some may be peculiar members of the mixed tumor group, or possible transformations of originally mixed tumors is an academic question too difficult to speculate about in the present paper. It is possible that some are lymphoblastomas, some granulomas; many have not been identified.

Some Tumors Mistaken for Mixed Tumors That Have Entered Into Our Material.

ANGIOMAS.

Non-recurrent.

No. 245. S. G., female, 10 months. An attempt was made to remove the angioma but the vessels were found to extend into the deeper tissues. The child died 2 days after operation.

No. 408. R. E. H., male, 5 months. This tumor had been present at birth. The entire parotid gland was removed. The patient is well and has had no recurrence in 13 years.

HÜRTLE CELL TUMORS (ONCHOCYTOMAS).

Non-recurrent.

No. 402. H. H., female, 74 years. For many years had a pea-sized tumor near the angle of the left jaw. It became tender and was therefore excised 2 years ago. Lost.

Recurrent.

No. 90. I. B., male, 89 years. The tumor existed for 3 years before it was operatively removed in 1923. I reported it as an adenoma, but 12 years later there was a recurrence that in the course of 6 years grew

to the size of a plum. The man died in 1941, at nearly 90 years of age, the tumor not having been removed and giving no trouble except slight pain on opening the mouth. It never ulcerated.

NEUROFIBROMA—SCHWANNOMA.

Non-recurrent.

No. 181. H. D., white female, 32 years. Had the tumor 5 years when it was excised. No recurrence in 7 years.

Recurrent.

No. 119. P. C., white male, 58 years; right side. Tumor first appeared in 1887 and was excised in 1895. In 1927 there was a recurrence. This was excised in 1931. In 1935 a second recurrence was reported. He now has facial palsy.

BRANCHIOGENIC CARCINOMAS?

Non-recurrent.

No. 359. L. H., black male, 66 years. Was admitted to the hospital with a tennis-ball sized swelling below the right mandibular angle. It was excised and proved to be an epidermoid carcinoma. No recurrence in 1 year. Lost.

Recurrent.

No. 77. J. D., white male, 51 years. For 4 months he had observed a small lump to the right of the midline of the neck. It grew rapidly, to the right, without pain, and was the size of an orange when excised. It recurred repeatedly and was excised 4 times at intervals of about 6 months. He died of the tumor 37 months after the last operation.

The glandular distribution of the mixed tumors was as follows: 2 sublingual, 12 submaxillary, 380 parotid.

As the position of the tumor is not always such as to permit the surgeon to be sure from which gland it arises, there may have been more submaxillary and fewer parotid tumors.

The sex distribution of the tumors was found to be as follows: males, 184; females, 212. There were 144 noted on the right side, 147 on the left. There was no case of bilateral tumors nor of simultaneous tumors in two different glands; there were a few multicentric tumors.

With the doubtful tumors excluded and with 400 accepted mixed tumors remaining, we find that their operative removal has been followed by recurrence in 100 (25%). This corresponds fairly well with what is usually stated in the books and might be permitted to stand, were it not for certain modifying circumstances. It is impossible to arrive at accurate percentages in the matter of recurrence, as will be evident from the following: Of the total of 400 cases, 96 have been lost to the follow-up without record of recurrence, so that no one is in a position to say whether they have suffered from recurrences or not. Deducting them from the total makes the percentage of recurrences rise to 32.5%. Suppose the "5-year rule," widely adopted in the study of cancer, be applied to the "mixed

tumors," and every case not under observation for 5 years be ruled out, what would then be the percentage of recurrences? Of our tumors still under observation, 30 have been for periods up to 4 years, but no longer. If we now deduct them, the recurrences rise to 36.4%. Furthermore, 66 of the patients from whom mixed tumors had been surgically removed have died without having suffered from the recurrences they might have had, had they lived longer. If we deduct them so that our calculation is based only upon those *cases still living and still under observation*, the percentage of possible recurrences rises to 48%.

But the average length of time that elapses between the operative removal of the primary tumor and its recurrence was shown in a previous paper to be 7 years, and if we consider only those cases that have been under observation for that period or longer, the possible recurrences rise to 62%.

In the study of oncology, nothing is more important than the complete history of the tumor from the time of its first discovery until its end with the death of the patient. Even then one should not be satisfied; a necropsy should be performed, the cause of the patient's death determined, and any part toward it contributed by the tumor carefully noted. All this requires persistent "follow-up" of the patients, year after year—a matter that is frequently attended by great difficulty.

The course of these tumors is often very tedious and the patients have ample opportunity to move from place to place, city to city, or even country to country, leaving no addresses behind. For instance, Case 85 (M. S.) was first operated upon in Odessa, Russia. Some years afterward she came to live in Philadelphia, where she underwent operations for the removal of recurrences in the Methodist, the Mt. Sinai, the Lankenau and the Philadelphia General Hospitals, where she died. Case 127 (M. D.) was first operated upon in St. Louis, Mo.; then moving to Philadelphia, was again operated upon in the Jewish, the Hahnemann, and the University Hospitals, after which she died of the tumor in the Lucian Moss Home. To follow peripatetic patients like these requires time, patience, perseverance, and sometimes expenditure of money.

But the reason for persisting in keeping track of the patient is evident when the vagaries of the tumor are kept in mind. Although a few of the tumors are said to recur "immediately," "at once," "very soon" or "shortly," the greater number show no new tumor growth for years. In our cases, the average period elapsing between the excision of the primary tumor and the discovery of a recurrence is about 7 years. It is impossible to arrive at an accurate figure for this interval because the patients never note the exact date of recurrence, but think of it as "6 months" or "a year" or "18 months" ago, and also because in many cases the only interval given on the protocol is that between successive operations.

But although 7 years is the average period, 10, 15, 20, 25, 30, 35, 40 and even 45 years may pass before recurrence comes about. This naturally raises the question whether anyone once the victim of a mixed tumor may ever be regarded as "well" and "completely out of danger."

Most of the mixed tumors are nodular, lobulated and encapsulated. Each lobule has its own capsule, while a general capsule surrounds the whole. It appears as though the tumors are often multicentric, each lobule separated from its neighbor, in the beginning, sometimes by a narrow interval, sometimes by a greater one. The greater the separation of the lobules, the longer the tumor must grow, and the larger the size it must attain before all parts become surrounded by the general capsule.

In a previous paper I made a careful study of the frequency of the recurrence of these tumors in relation to their size at the time of primary excision. It showed that when the tumors removed were smaller than a lemon, about twice as many recurred as when they were larger than a lemon. It would, therefore, seem as though the smaller tumors offered a greater opportunity for the surgeon to overlook the still separate, small, outlying lobules, than the larger ones. But, of course, other factors, such as the nature of the tumor, undoubtedly influence recurrence.

The patient afflicted with the tumor and the surgeon who operates upon it always want to know the probability of recurrence, and in no other field does there seem to be such contradictory prognostic evidence as among the mixed tumors. One has a structure that suggests no further trouble, yet the tumor quickly recurs; another presents all the appearances usually thought to indicate a malignant disposition, yet after excision nothing happens. I have suffered such repeated mortification and embarrassment through predicting

LEGENDS FOR FIGS. 1 TO 6.

FIG. 1.—Simple interstitial tumor complicated by an excess of cells. Case 124. A. R., aged 51, white. Tumor of 40 years' duration. The tumor recurred after an interval of 7 years and was again excised, since which there has been no recurrence in 11 years.

FIG. 2.—Simple interstitial tumor with occasional areas suggesting carcinoma. Case 338. I. S., male, aged 44. The tumor recurred in 10 years, then again in 3 years.

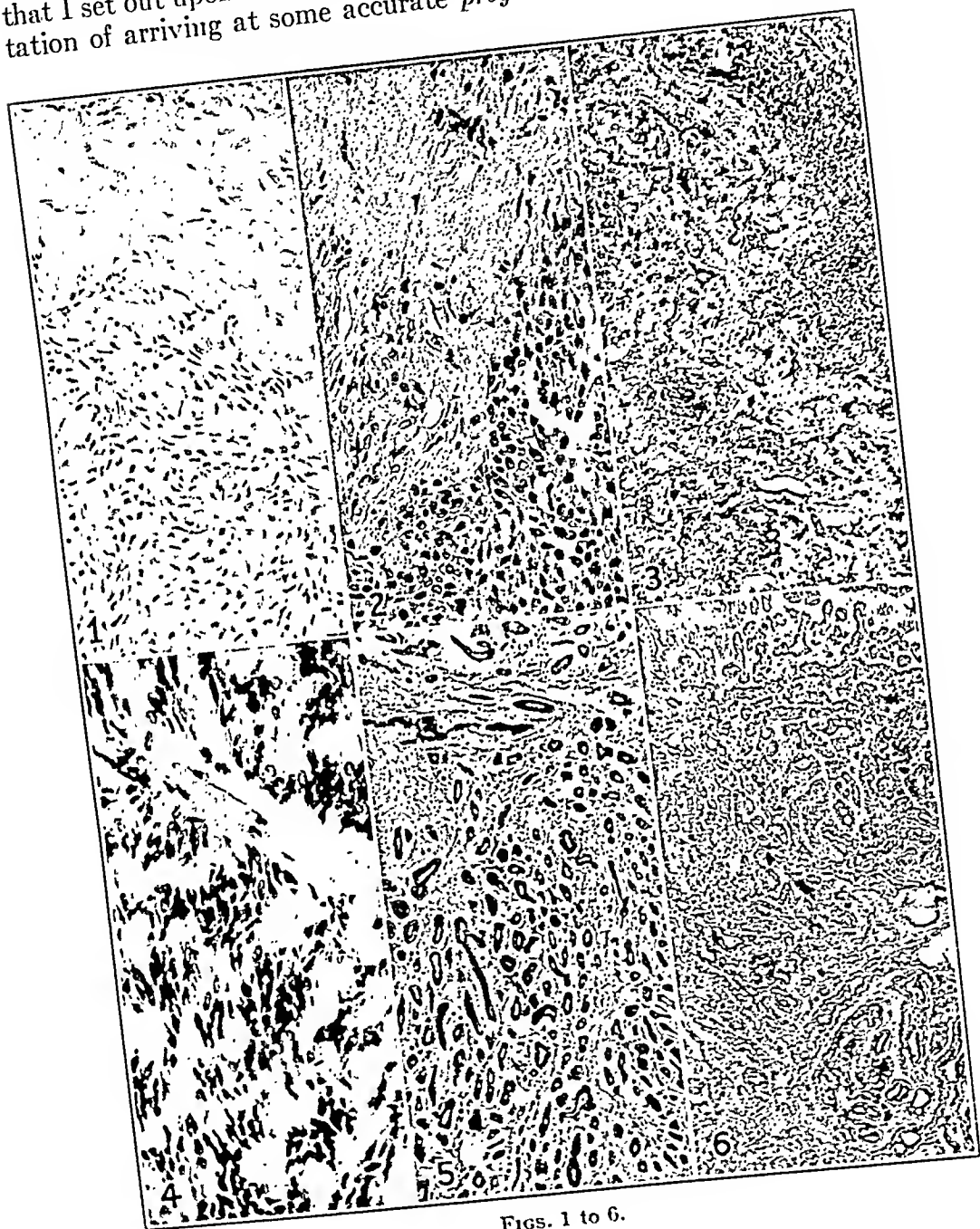
FIG. 3.—Cylindroma of the parotid gland. Case 135. Dr. E. P. McN., white, aged 43. The known duration of the tumor was 3 to 4 years. There has been no recurrence in 6 years.

FIG. 4.—Cylindroma of the parotid gland. A. W., white male, aged 74. The tumor was of 6 years' duration and the size of a baseball. It had not recurred 5 years after operation.

FIG. 5.—Simple canalicular tumor. Case 232. M. M., female, white, aged 47. The tumor had been known to be present in the right sublingual gland for 3 years. It recurred 3 months after excision.

FIG. 6.—Simple canalicular type of tumor. Case 214. Mrs. I. E., white, aged 57. The tumor was of 6 to 8 years' duration, recurred in 2 years after excision. There has been no further recurrence during 3 years after the second operation.

what these tumors will do, only to find myself wrong about them, that I set out upon this investigation in the earnest hope and expectation of arriving at some accurate *prognostic histologic* indication.



FIGS. 1 TO 6.

The best that I had previously been able to do was expressed in a former paper,^{1a} as follows: "When the pre-operative duration is expressed in months and the histological appearance resembles carcinoma, the prognosis is bad." It might be conversely con-

cluded: "When the pre-operative duration is expressed in years and the histological appearance presents no resemblance to cancer, the prognosis is good." I wish that that were true, but, unfortunately, of the latter tumors 33% recur.

As the reader is doubtless familiar with the histology of the more common varieties of the mixed tumors, the details need not be repeated. But different lobules of the same tumor sometimes show entirely different structure. Such being the case, the examination of one or another lobule, as accident might determine, might lead to the tumor being classified one way or another with different prognostic conclusions. This may account for some of the seemingly inconsistent and perplexing behavior of the tumors. But no pathologist can examine every part of every tumor; he must routinely be satisfied with at best the examination of a few sections and form his opinion from them.

When such examinations are made the tumors can be divided, not scientifically but conveniently, into two main groups, in one of which the interstitial type of tissue—mucoid, chondroid, hyaline, and so on—preponderates, and in the other of which the parenchymatous or epithelial type preponderates. There is no sharp line of distinction between the two and the placing of a tumor in one or the other class is a matter of judgment. In either case, however, there are additional points of interest that may attract attention and bear upon the prognosis, such as an unusual abundance of the small spindle cells, the unexpected presence of epidermal cells with prickles and of occasional epithelial pearls, an unusual amount of the gland-like elements that are almost always to be found upon the surfaces of the lobules of the interstitial tissue tumors, or between their lobules, and the appearance of dilatations

LEGENDS FOR FIGS. 7 TO 11

FIG. 7.—The canalicular papillary tumor. Case 220. Mrs. L. D., white, female, aged 62. The preoperative duration of the tumor was only 1 month. It was operatively removed 5 times in 4 years, recurring each time. It finally caused the death of the patient though it produced no metastasis.

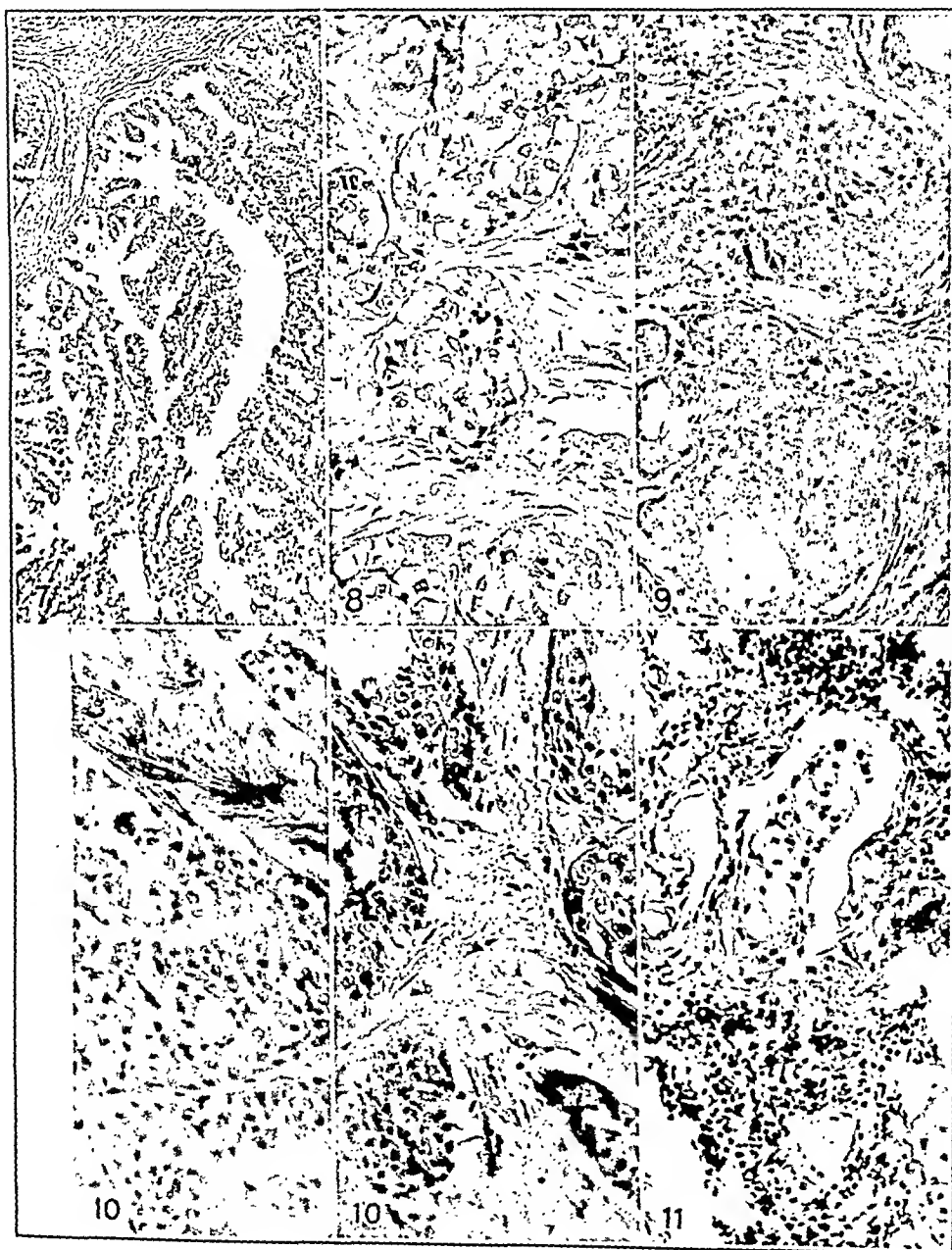
FIG. 8.—Canalicular and carcinomatoid tumor. Case 59. M. R., white, female, aged 45. The tumor in the left parotid gland was of 5 to 6 years' duration. She had several excisions followed each time by recurrence, the last growing large, entering the orbit and invading the cranial cavity with fatal pressure. There was no known metastasis.

FIG. 9.—A carcinomatoid tumor. Case 94. P. L. was a "little girl." Following excision of the tumor, there has been no recurrence in 7 years.

FIG. 10.—Canalicular tumor, with a few areas like that in the illustrations that appear carcinomatous. Case 306. A. G., aged 49, white, female. For two months had observed a small tumor below the left ear. When it was as large as a chestnut she had it excised. There has been no recurrence in 3 years.

FIG. 11.—A mixed tumor metastasis in a cervical lymph node. Case 115. S. G., white, female, aged 15. There has been no return of the tumor 5 years since the last excision.

of the ducts and canaliculi of the parenchymatous variety, with occasional papillary growths extending into them, or the loss of the regular tubular pattern and an appearance suggesting carcinoma.



FIGS. 7 to 11.

This convenient arrangement has been adopted in the following lists and tabulations:

TABLE 1.—GROUP A-I. THE SIMPLE INTERSTITIAL MIXED TUMORS WITHOUT HISTOLOGIC ELEMENTS SUGGESTING MALIGNANCY.

a. Non-recurrent.

Case.	Name.	Sex.	Age.	Color.	Side.	Preop. duration (yrs.).	Size.	Postop. freedom (yrs.).	Remarks.
1	H. S.	M	24	W	R	8	Walnut	26	
2	W. R.	M	59	W	R	8	Egg	8	
3	A. R.	F	63	W	L	$\frac{1}{2}$	Orange	5	Died of pneumonia.
4	F. H.	F	19	W	L	3	"Small"	5	Died of pul. tb.
5	M. E.	F	62	W	R	32	..	16	Lost at 78 yrs.
7	E. N.	F	49	W	R	17	
9	A. McC.	F	48	W	L	20	...	14	
11	H. H. P.	F	52	W	R	8	...	8	Died of heart attack.
12	A. R.	F	32	B	R	4	..	23	
14	J. Q.	F	58	W	L	25	..	17	
18	E. S.	M	31	W	..	$\frac{1}{2}$	Plum	10	Died of appendicitis.
22	B. D.	F	39	W	R	10	...	11	
23	E. L.	F	42	W	13	
27	E. N.	F	50	W	..	7-8	...	15	
34	E. M.	F	65	W	L	32	...	18	
35	W. H.	M	33	B	..	6	...	15(7)	
39	C. J.	M	47	W	L	7	...	13	
42	M. H.	M	62	W	R	32	...	3	Died of diabetes.
44	N. K.	M	28	W	R	4	...	4	Lost.
62	A. C. C.	F	51	W	L	15	..	15	
64	L. C.	M	54	W	L	24	...	9	Lost.
95	B. B. P.	M	64	W	R	28	...	13	Suicide.
100	J. W.	M	37	W	L	5	...	2	Lost.
103	L. H.	F	43	W	..	2	...	32	
105	C. B. N.	M	34	W	..	$1\frac{1}{2}$...	23	
128	J. R.	M	34	B	L	10	...	8	
133	A. L.	F	31	W	R	8	...	7	
136	G. M. T.	M	66	W	L	2	...	6	
145	R. L.	F	..	W	2	
150	W. H.	M	43	W	L	"Some time"	...	5	Lost.
152	C. K.	F	32	W	L	10	...	6	
161	M. A.	F	68	W	..	10	...	7	
163	E. S.	M	23	W	R	4	Hen's egg	11	
173	W. H.	M	50	W	..	2	Pea	10	
209	C. M.	F	37	B	L	$1\frac{1}{2}$	Egg	3	
217	E. B.	F	51	W	R	$\frac{1}{2}$	Walnut	5	
219	S. G.	F	26	W	L	4	Walnut	5	
222	M. L.	M	45	W	R	6	Lemon	7	
227	M. McN.	F	41	W	L	7	Pigeon's egg	7	
228	E. B.	F	43	W	R	1	...	4	
240	E. R.	F	26	W	..	6	...	4	
248	M. C.	F	26	W	L	$1\frac{1}{2}$..	9	
263	S. S.	M	36	W	R	..	Walnut	5	
264	S. S.	F	50	W	L	6	...	7	
271	J. S.	M	59	W	L	30	...	7	Died.
275	I. D.	F	29	W	L	7	
281	J. G. K.	M	27	W	L	?	...	7	
283	W. M.	M	..	W	6	
286	E. M.	F	41	W	R	3	...	11	
293	F. S.	M	60	W	R	20	...	10	
302	J. D.	M	38	W	L	8	...	7	
303	G. W.	M	34	W	L	3	...	3 to date	
304	F. C.	M	26	W	L	$1\frac{1}{2}$	Walnut	3	Lost
313	W. R.	M	21	W	L	10	Walnut	5	
314	R. H.	M	28	W	L	1	Grape	3 to date	
341	V. B.	F	42	W	L	2	Apple	1 to date	
342	H. B.	M	55	W	L	2	...	3 to date	
350	M. B.	F	50	W	3 to date	
352	A. C.	M	45	W	L	$\frac{1}{2}$...	3 to date	
357	A. H.	M	35	W	L	10	...	3 to date	
361	H. A.	F	48	W	..	12	..	5 to date	
382	M. B. T.	F	53	B	R	10	...	4 to date	

b. Recurrent.

Case.	Name.	Sex.	Age.	Color.	Side.	Preop. duration (yrs.).	Size.	Postop. freedom (yrs.).	Remarks.
6	S. H.	F	25	W	L	7	...	29	
16	F. S.	M	22	W	R	10	...	7	
51	E. daC.	F	35	W	..	3	...	14	First excision in 1904; 1st rec. excised in 1918; 2d rec. excised in 1924; 3d rec. ex- cised in 1929.
53	V. C.	F	23	W	L	6	Walnut	Rec. at once	Lost.
58	G. S.	M	39	W	L	16	...	2	Died of Bright's dis- ease 22 yrs. later.
60	H. S.	M	29	W	..	8	Little lump	1	Lost.
61	A. C.	M	25	W	R	6	Almond	Rec. in 17	
93	H. A.	M	27	W	..	2	...	Rec. in 5, 6 and 8	Lost.
122	M. K.	F	42	W	R	8	Thumb nail	$\frac{1}{2}$	Lost.
141	B. S.	F	20	W	L	1	Walnut	6	
146	F. B.	F	30	W	L	Part of 1	Walnut	5	
154	E. W.	M	45	B	R	7	Still has it 5 yrs. after.
156	K. S.	M	22	W	L	..	Small egg	-1	
158	J. S.	M	L	Rec. no data	Lost.
167	B. W.	M	..	W	..	36	..	Rec. at once	Free for 5 yrs.
178	F. S.	F	30	W	R	2	...	4, then no rec. in 7	
182	R. L.	F	39	W	R	7	Hen's egg	$\frac{1}{2}$	
189	E. H.	F	..	W	L	10	Lemon	5	Lost.
192	S. K.	F	..	W	L	8	Walnut	1	Lost.
193	T. S.	M	..	W	R	..	Large orange	13 and 21	Died of pneumonia.
205	D. J.	F	34	W	R	?	...	3	Had 2d excision.
226	A. O'N.	F	..	W	R	Rec. at once; still has it	Lost.
230	W. M.	M	R	3	Lost.
234	C. K.	F	60	W	..	2	Walnut	Rec. "soon after"	
298	J. K.	M	43	W	L	2	Walnut	$\frac{1}{2}$	Lost.
346	W. R.	M	..	W	L	12	Lemon	12	Lost.
366	E. K.	M	56	W	..	10	Walnut	10	
367	B. B.	M	18	W	L	2 $\frac{1}{2}$...	$\frac{1}{2}$	
368	M. F.	F	55	B	R	6	..	-1	
369	M. O.	M	55	W	..	2	...	Rec. after 21	No rec. after 2d excis.
370	R. S.	F	43	W	L	Many	Walnut	2	
380	T. B.	M	20	..	R	2	...	Rec. after 10	Still has the tumor.
381	G. M.	M	34	W	R	No data	...	Rec. in 8 mos.	Still has the tumor.
384	I. L.	F	28	W	R	3	...	Prob. rec. in 3	
406	W. F.	M	48	W	R	No data	...	Rec. in a few mos.	Second operation in 7 yrs.

TABLE 2.—GROUP A-II. THE SIMPLE INTERSTITIAL MIXED TUMORS WITH SUSPICIOUS ELEMENTS.

1. TUMORS WITH AN UNUSUAL PROPORTION OF CELLS.

a. Non-recurrent.

Case.	Name.	Sex.	Age.	Color.	Side.	Preop. duration (yrs.).	Size.	Postop. freedom (yrs.).	Remarks.
151	G. H.	M	56	W	R	25-30	...	9	
166	G. E.	F	40	W	R	12	...	3	Died.
238	A. M.	F	46	W	L	1+	Lost.
278	C. H.	F	20	W	..	?	...	30	
304	F. C.	M	26	W	..	1 $\frac{1}{2}$...	3	
386	E. G.	F	67	W	L	Several	...	4 to date	

b. Recurrent.

51	E. daC.	F	35	W	Rec. in 3, 10 and 3, then free for 12	Lost.
124	A. R.	M	51	W	L	40	...	Rec. in 20	
162	C. F.	F	56	W	R	1	...	Has rec. now	

2. TUMORS IN WHICH OCCASIONAL, RARE GROUPS OF SQUAMOUS EPITHELIUM WERE FOUND, SOME WITH "PRICKLES," OR EPITHELIAL PEARLS.

a. Non-recurrent.

Case.	Name.	Sex.	Age.	Color.	Side.	Preop. duration (yrs.).	Size.	Postop. freedom (yrs.).	Remarks.
19	M. McL.	F	26	W	..	3	...	15	
21	L. B.	F	32	11	
25	C. K.	F	30	B	.	12	Egg	13	
26	A. C.	M	35	W	L	4	Walnut	9	Lost.
199	S. E.	F	16	W	L	$\frac{1}{2}$	Hickory nut	7	
262	H. R.	F	65	W	R	3	Brazil nut	5	
272	L. B.	F	75	W	R	20	Lost.
347	M. B.	F	19	W	2	
354	M. M.	F	28	W	L	1	Marble	2	

b. Recurrent.

50	C. B.	F	86	W	Olive to orange	30	Died.
52	A. S.	F	23	W	R	-1	Almond	7	Still has it.
169	B. Z.	F	42	W	L	9	
172	J. M.	M	19	W	Came in with a recurrence.
319	H. S.	M	37	W	13	

3. TUMORS IN WHICH SOME OR ALL OF THE STROMA, INSTEAD OF BEING MUCOID OR CHONDROID, CONSISTED OF COARSE HYALINE MORE OR LESS PARALLEL BUNDLES, BETWEEN WHICH THE CELLULAR AND GLANDULAR ELEMENTS ARE COMPRESSED; *Cylindroma* IN BILLROTH'S SENSE.

a. Non-recurrent.

135	E. P. M'N.	M	43	W	..	3-4	Olive	6	
297	A. W.	M	74	B	R	6	Baseball	5	
385	J. T.	M	65	W	R	4	Lemon	Primary tumor not entirely ex- cised unchanged for 4	

b. Recurrent.

37	J. H.	M	77	W	L	10	...	2	
46	A. M.	F	36	W	L	9 $\frac{1}{2}$	Still has tumor
48	B. B.	F	39	W	R	20	Plum	12	Lost.
139	M. K.	M	50	W	L	2	
148	J. P.	M	46	W	L	16	..	free for 7 Rec. in, 3, 7, 10, no further rec.	
337	Dr. G.	F	44	W	..	25	Lemon	5 20	

4. TUMORS IN WHICH THE PARENCHYMATOUS OR GLANDULAR ELEMENTS WERE CONSPICUOUS COMPONENTS, WITHOUT ACTUALLY ALTERING THE GENERAL TYPE OF THE TUMOR.

a. Non-recurrent.

20	H. D.	F	44	W	R	15	...	13	
24	J. D.	M	42	4	Lost.
239	M. F.	F	45	W	L	1	Hickory nut	4	
280	R. H.	M	33	W	L	9	
314	R. H.	M	28	W	L	1	Grape	3	

b. Recurrent.

45	B. C. R.	M	43	W	L	16	...	21	
49	H. B. W.	F	Rec. in 7, 4, 12 free for 12	
171	A. F.	F	47	W	L	27	...	Rec. in 1, 5, 1	Lost.
273	H. B.	M	56	W	L	15	Plum	5	No rec. in 10 yrs.

5. TUMORS IN WHICH SOME SMALL AREAS HAVE SUFFICIENT RESEMBLANCE TO CARCINOMA TO ATTRACT ATTENTION AND AWAKE THE SUSPICION OF MALIGNANT CHANGE.

a. Non-recurrent.

Case.	Name.	Sex.	Age.	Color.	Side.	Preop. duration, (yrs.).	Size.	Postop. freedom (yrs.).	Remarks.
33	L. D.	M	46	W	L	4	Grape	4	Died.
136	G. M. T.	M	66	W	L	2	Hickory nut	6	
210	E. W. F.	F	..	W	2	Died.

b. Recurrent.

52	A. S.	F	23	W	R	4	Almond	7	Had rec. for 10 yrs.
298	K. K.	M	..	W	L	2	Walnut	1, then in 10, 3	Lost.

6. TUMORS WHOSE UNUSUAL RICHNESS IN SPINDLE AND SPIDER CELLS SUGGESTS BEGINNING SPINDLE CELL SARCOMA OR MYXOSARCOMA.

a. Non-recurrent.

215	G. O.	M	20	W	R	5	Walnut	5	
307	C. M.	F	39	W	L	1½	4½ cm.	5	

b. Recurrent.

55	M. Z.	F	64	W	R	20	2 fists	1½	Died of rec. in 8 yrs.
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7. TUMORS IN WHICH OSTEOID OR OSSEOUS TISSUE WAS PRESENT.

a. Non-recurrent.

190	M. Die	F	23	W	L	½	...	1	Lost.
229	L. A.	F	18	B	R	18	Egg	..	Lost.
347	M. P. B.	F	19	W	..	1	...	2	

TABLE 3.—GROUP B. THE CANALICULAR TUMORS.

(These are tumors whose structure is largely parenchymatous, glandular and canalicular. Some are made up of simple tubules, some of dilated tubules with complex vegetations, some have the parenchymatous elements so compacted and crowded together as to present a carcinomatoid appearance.)

1. THE SIMPLE CANALICULAR TUMORS,

a. Non-recurrent.

Case.	Name.	Sex.	Age.	Color.	Side.	Preop. duration (yrs.).	Size.	Postop. freedom (yrs.).	Remarks.
99	A. G.	F	73	W	L	20	Olive	5	Lost
117	C. P. P.	F	40	W	L	2	2½ x 2½ x 1½ cm.	7	
140	R. R.	F	81	20	Died in 1 yr. of other causes than tumor.
214	I. E.	F	55	W	R	6-8	..	4	
210	E. R.	F	26	W	..	6	..	4	
269	L. T.	F	50	W	L	1 ?	..	5	
306	A. G.	F	49	W	L	1	Walnut	7	
411	N. S.	M	Long	Sublingual; operated on a few mos. ago.

b. Recurrent.

122	M. K.	F	42	W	R	8	Thumb nail	½	Lost.
171	A. F.	F	47	W	L	27	..	Rec. 3 times in 7	Lost.
232	M. M.	F	47	W	R	3	Lemon	1	Lost.
270	B. J.	F	22	W	..	1½	Walnut	½	Sublingual.
317	B. H.	F	60	W	L	?	...	Rec. 3 times	No recurrence since 1936.
518	J. S.	F	76	W	R	41, again in 9	
537	G's case	F	44	W	..	25	Lemon	Rec "shortly"	In 20 yrs. has grown to size of cantaloupe; excised again.
599	M. G.	F	4	...	2	Lost.
421	J. S.	F	No data	Only rec. is known to us.

2. THE INTRACANALICULAR PAPILLARY TUMORS.

a. Non-recurrent.

Case.	Name.	Sex.	Age.	Color.	Side.	Preop. duration (yrs.).	Size.	Postop. freedom (yrs.).	Remarks.
222	M. L.	M	45	W	R	6	Lemon	7	
334	A's case	F	31	W	..	$\frac{1}{2}$	1 $\frac{1}{2}$ in.	4	

b. Recurrent.

78	H. M.	M	62	W	R	$\frac{1}{2}$	Died of tumor in about 7 yrs.
85	M. S.	F	43	3 rec. in 24	Died of tumor.
104	M. S.	F	21	5	..	2 rec. in 5	
127	M. D.	F	41	27	..	5 oper. for rec.	Died of tumor.
153	F. M.	M	41	..	L	20	...	2 oper. for rec.	Lost.
206	M. S.	F	37	5	
220	M. D.	F	..	W	R	$\frac{1}{12}$	Walnut	Various	Oper. after 6 mos., 2 yrs., 3 mos., 9 mos.; died 1 yr. later.
232	M. M.	F	47	W	R	3	Almond	$\frac{1}{2}$	Lost.
333	L. M.	F	20	W	L	2	...	1	Died of tumor.

3. THE CARCINOMATOID CANALICULAR TUMORS, THAT RESEMBLE CARCINOMA TO SUCH AN EXTENT THAT IT MAY BE IMPOSSIBLE TO AVOID CONFUSION.

a. Non-recurrent.

94	P. L.	F	Little girl	W		
202	C. B. R.	F	37	W	L	1	Almond	9	Six yrs. after excision "lump appeared but completely disappeared under x-rays."
308	G. C.	F	50	W	R	2	Egg	6	

b. Recurrent.

59	M. R.	F	45	W	..	5-6	Walnut	Rec. in $\frac{1}{2}$ 1, 2	Died of tumor.
115	S. G.	F	10	W	L	5 oper. in 6	Well 6 yrs.
236	M. C.	F	50	W	R	6	...	Rec. in a few mos., 2, 1, 1	

TABLE 4.—GROUP C. THE CARCINOMATOID MIXED TUMORS.

(I have employed this term to include tumors arising, supposedly, in the salivary glands and so closely resembling carcinomas as usually to be classified as such. Though some listed below may be carcinomas, they differ strikingly in the particulars pointed out.)

I. THE TUMORS MAKE THEIR APPEARANCE AT A VERY EARLY AGE.

Case 115. S. G., white female. The tumor first appeared at 7 years. She has had 4 operations for its removal, and has had treatments by Roentgen rays and radium packs. She is now 21 years old, and has been without recurrence for 6 years, is in good flesh, works as a laboratory technician and is regarded as "cured."

Case 127. M. D., white female. The tumor was discovered at 4 years. She died at the age of 42, having in the course of 38 years, undergone 6 operations for the excision of the tumor and its recurrences, several courses of Roentgen ray treatments, radium applications, division of the fifth nerve root for the relief of pain, and having long had facial palsy. The tumor never metastasized, though it caused her death.

Case 197. E. S., white female. The tumor was first observed in early childhood, and was first treated when she was 10 years old. During the next 45 years "various attempts at removal were made without success as the tumor always recurred." The last operation was in 1935, since when she has "had no more trouble."

II. THE TUMORS MAY HAVE AN EXTREMELY LONG PREOPERATIVE DURATION.

This may support the theory that a "benign mixed tumor," "becomes malignant" or undergoes "malignant degeneration."

Case 88. M. H., white female, had a small tumor of some kind, "cheese tumor," removed from the parotid region, and 15 years afterward applied for treatment because of a recurrence the size of an orange. This was treated by radium. After 2 years, 2 nodules, supposed to be metastatically invaded lymph nodes, were found in the submaxillary region, and the fluoroscope showed some kind of nodules in the lungs. She died 3 years later, at home, and no necropsy was performed. She will again appear under carcinomas.

Case 191. G. F., white male, he had a small "parotid cyst" removed, and 15 or 18 years later came to the hospital with a tumor the size of a lemon, situated in the same place. This was excised. He died, at home, 2 years later, but no necropsy was performed.

Case 252. W. K., white male, had a tumor on the right side of his face for 15 years before removal. The recurrence seems to have been a carcinoma and will again appear under that heading.

III. THE TUMORS, UNLIKE CARCINOMAS, ARE RARELY METASTATIC.

Case 86. Mrs. S. L., white female of 68, had a carcinomatoid canalicular tumor, and was said to have metastasis to the cervical lymph nodes. The tumor was excised, recurred and was again excised in less than a year. She died 10 months later, at home. No necropsy.

Case 88. M. H., white female, was considered in Section II, with the reason for thinking that the tumor was probably metastatic.

Case 115. S. G., white female, of 21 (see Section I), had an undoubted metastasis in a cervical lymph node. Histopathologists differed as to whether it was a "mixed tumor" metastasis or a carcinoma metastasis. If the latter, it is unusual at as early an age as 15 years, and it is equally unusual for 6 more years to pass without new signs of the presence of the tumor.

Case 333. Mrs. L. M., white female, of 21, had an intracanalicular papillary mixed tumor of the parotid, for which she was operated upon. Facial palsy resulted, followed by recurrence of the tumor in about a year. A second operation was followed by a second recurrence. A third operation was performed, and enlarged cervical lymph nodes were also removed. The latter showed only inflammation, no metastasis. A short time after the last operation she became unconscious, remained so for 7 days, then died. Her family physician interpreted the unconsciousness as due to cerebral metastasis, but of this there is no proof, as there was no necropsy. It might have been due to embolism or to apoplexy.

IV. SURGICAL EXCISION IS SOMETIMES FOLLOWED BY APPARENT "CURE."

Case 8. E. C., white female, of 56; 6 years. Walnut size. Died of pulmonary tuberculosis 5 years later, without recurrence of the tumor, microscopic sections of which were thought to be "carcinoma."

Case 73. J. McG., white male, of 21; 2 years. For 2 years had a lump in the right side of the neck at the angle of the jaw that was thought to be tuberculous lymph nodes. Excised and examined microscopically, it was found to be "carcinoma." The patient never had any recurrence or further local trouble and died of pulmonary tuberculosis 7 years later.

Case 74. D. C., white female, of 30; 1 year. Right side, 6 cm. in diameter. The tumor was excised, had a structure suggesting an anaplastic squamous carcinoma. The patient is living and well 15 years later, without recurrence.

Case 76. J. D., white male, of 50; 2 years. Egg-sized. Excised and recurred within a year. After a second excision there was no recurrence in 20 years, the patient still living and well. Metastasis was observed in cervical lymph nodes, exactly like that in Case 115, and was regarded as carcinoma metastasis. Upon later and more careful examination, however, they were found to be "mixed tumor metastasis."

TABLE 5.—GROUP D. THE SARCOMATOIDS OF THE SALIVARY GLANDS.

1. RESEMBLING MYXOSARCOMA.

a. Non-recurrent.

Case.	Name.	Sex.	Age.	Color.	Side.	Preop. duration (yrs.).	Size.	Postop. freedom (yrs.).	Remarks.
307	C. M.	F	39	W	L	1	4½ cm.	6	
70	I. B.	F	65	..	R	2	Orange	Nn rec. in 10	

b. Recurrent.

54	M. H.	F	55	B	L	4 ?	Egg	13	Was again excised, with rec. and lived a number of years; died of pneu- monia at home; no necr.
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2. RESEMBLING SPINDLE CELL SARCOMA.

a. Non-recurrent.

215	G. O.	M	20	W	R	5	Walnut	5	
68	P. W.	F	34	W	R	3	Walnut	5	

b. Recurrent.

55	M. Z.	F	64	W	R	20	...	1½	After trauma tumor grew very rapidly and killed in 6 yrs.; no necr.
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3. RESEMBLING LYMPHOSARCOMA.

Non-recurrent.

67	L. F.	F	28	W	L	½	...	20	
69	C. T.	F	40	W	L	6	...	10	

The outcome seems to show that the tumors were not sarcomas, as reported, but something less important.

TABLE 6.—CARCINOMAS.

NON-METASTATIC.

Recurrent.

Case.	Name.	Sex.	Age.	Preop. duration (yrs.).	Remarks.
79	J. M. M.	M	62	1½	Died of tumor within 1 yr.
81	E. C.	M	75	½	Died in 3 yrs.
82	W. W. VanD.	M	52	5	Died—date unknown.
87	A. C.	M	60	3	Died, date unknown; sq. cell carc.?
185	J. B.	M	59	1½	Lost.
218	J. G.	M	41	½	Died in 2 yrs.
299	C. H.	F	60	3	Died in 1 yr.
324	J. N.	M	65	½	Died few months after operation with a grapefruit-sized tumor.

METASTATIC.

Recurrent.

86	S. L.	F	68	1	Died; metastasis to cerv. lym. nodes.
88	M. H.	F	65	2	Died in 2 yrs.; thought to have had metastasis to cerv. lym. nodes and lungs; no necr.; no excisions.
116	A. K.	F	70 (B)	7-10	Grapefruit-sized primary tumor; died soon after Roentgen ray treatments were begun; metastasis in cerv. lym. nodes.
252	W. K.	M	68	15	Lived only 2 yrs. after oper.; had metastasis to cerv. lym. nodes.
333	L. M.*	F	20	2	Died in 1 yr. after 2 rec. and was supposed to have had metastasis to brain but there was no post-mortem proof.

It should be noted that a satisfactory proof of metastasis is given in only Cases 86, 116 and 252. A striking contrast obtains between the metastasis in the mixed tumor, as in Cases 78 and 115, who have lived for years after the metastasis had occurred, and the carcinoma cases, all of whom with the exception of Case 185 are known to have died of the tumor.

TABLE 7.—THE PERCENTAGE OF RECURRENCES IN EACH GROUP.

GROUP A-I (Table 1).—The Simple Interstitial Tissue Mixed Tumors:

Totals.	Non-recurrent.	Recurrent.		No. of cases proving fatal.
		No.	%.	
97	62	35	34.2	0

GROUP A-II (Table 2).—The More Complex Interstitial Tissue Tumors:

	Totals.	Non-recurrent.	Recurrent.		No. of cases proving fatal.
			No.	%.	
1	9	6	3	33.0	0
2	14	9	5	35.7	0
3 (cylindroma)	9	3	6	66.0	0
4	9	5	4	44.4	0
5 (carcinomatoid)	6	3	3	50.0	0
6	3	2	1	33.3	0
7	3	3	0	0.0	1
Totals	150	93	57	38.0	1

GROUP B (Table 3).—The Racemose and Canalicular Mixed Tumors:

	Totals.	Non-recurrent.	Recurrent.		No. of cases proving fatal.
			No.	%.	
1	17	8	9	53.0	0
2 (papillary intra-canalicular)	11	2	9	81.8	4
3	6	3	3	50.0	1
Totals	34	13	21	60.0	5

GROUP C (Table 4).—The Carcinomatoid Mixed Tumors:

Totals.	Non-recurrent.	Recurrent.		No. of cases proving fatal.
		No.	%.	
13	3	10	76.0	6

GROUP D (Table 5).—The Sarcomatoid Mixed Tumors:

Totals.	Non-recurrent.	Recurrent.		No. of cases proving fatal.
		No.	%.	
8	6	2	25.0	1

CARCINOMAS (Table 6):

Totals.	Non-recurrent.	Recurrent.		No. of cases proving fatal.
		No.	%.	
13	0	13	100.0	13

GRAND TOTALS:

	All varieties.	Non-recurrent.	Recurrent.		No. of cases proving fatal.
			No.	%.	
Cases repeated	4	0	3	46.2	26 (12.8%)
	218	115	103	46.2	
	214	115	109	46.2	

In studying these statistics it is interesting to see that there is very little difference in the frequency of recurrence between the whole group of Interstitial or Simple Mixed Tumors (38%) and the Simple Mixed Tumors devoid of "suspicious" elements (34.2%) and that the only substantial increases are in Group 3, the Cylindromas (Billroth type) (66%) (in which, however, epithelial elements play no rôle) and Group 5, the Semi-canalicular tumors (50%).

But between the Interstitial Tumors (Group A) and the Parenchymatous or Epithelial Tumors (Group B) there is an enormous difference in the frequency of recurrence—38% in the former and 60% in the latter. The highest percentage of recurrences occurs in the Papillary Canalicular Group—81.8%. It is even higher than in Group C, the Carcinomatoid Group, where it is 76%.

Of the 57 interstitial or simple mixed tumors that recurred, it is interesting to find that with the exception of Case 55 (M. Z.; 64), whose tumor resembled a spindle cell sarcoma, and appears in Group A 6 and again in Group D, not one is said to have died of the tumor although several of them suffered repeated recurrences. In Group B 1, the Simple Canalicular Tumors, we have no data as to what became of 5 out of the 9 recurrent cases; but it is noteworthy that in Case 337 (44), the tumor was present for 25 years before it reached the size of a lemon and was excised, after which it recurred and grew in 20 more years to the size of a cantaloupe, when it was again excised 2 years ago. All this is in marked contrast with Group B 2, the Intracanalicular Papillary Tumors, that caused the death of 4 of the 9 patients.

It might be expected that Group B 3, the Carcinomatoid Canalicular Tumors, would yield the highest percentage of recurrences and deaths because of the possibility that some of them might have been carcinomas. However, the percentage of recurrences here is only 50%, and 4 of the 6 cases are living and free of the tumor after 6 years or more.

Death follows the development and progress of mixed tumors in such manner as to show that it is not from carcinoma. A recurrence may continue for years, gradually growing larger, and doubling its size every 5 years or so, or it may grow rapidly and frighten both the patient and the surgeon, so that it is soon subjected to another, then perhaps to still other excisions over a period of years; or the slowly growing tumor may meet an accidental traumatism that is followed by rapid enlargement terrifying to the patient. Such enlargement *may* result from tumor growth, but often depends upon internal hemorrhage, necrosis, edema, ulceration or suppuration. In a few cases extensions of the tumor have invaded the maxillary sinus, the orbit, the pharynx and have even effected an entrance into the cranial cavity to cause death by cerebral compression. With

large, ulcerated, sloughing and infected tumors, the patients go slowly down hill, and hemorrhage from the ulcerated lesions may bring about the fatal termination. But the tumor almost invariably remains local and metastasis is very rare. Indeed, it is only known to have occurred in 2 of the cases that we still regard as mixed tumors: namely, Cases 78 and 115. If let be, the tumor may grow to an enormous size—Cotterill's patient had a tumor nearly twice the size of his head and estimated to weigh about 22 pounds, yet was without external ulceration or metastasis.

It will be remembered that the purpose of the present studies was to find criteria by which the examination of a microscopic section, supplemented by the case history, might enable the histopathologist to make a reasonably accurate prognosis. We have endeavored to discover these criteria by calculating the variation in the percentages of recurrences attendant upon certain small and great differences in the structure of the tumor, but have not succeeded. Remembering that the great differences in the time elapsing between the primary operation and the recurrence in different cases precludes accuracy in the results, we are now ready to inquire whether there has been any gain in prognostic ability.

To determine this, microscopic slides from about 50 histologically varying tumors were given, without identification, to 25 competent microscopists by whom they were carefully studied, and notation made as to the probability of the recurrence of each. The protocol of each case was then compared with the opinion expressed. The prognosis was correct in an average of 52% and in error in 48%. Five of the group were pathologists of professorial rank; all of the others were teachers of pathology or directors of hospital laboratories. The professors did no better than the others. There was disagreement of opinion in the case of every slide. The two highest percentages of accurate results were 63%. In looking over the opinions of these two, one a professor of pathology, the other an experienced hospital laboratory director, it was found that they agreed upon a number of the cases, but it was also amusing to find that of these agreements, half of the opinions were wrong.

Conclusion. From the present study it appears that something more than a simple microscopic examination of a section of tissue will be required before an accurate prognosis of a mixed tumor of the salivary glands becomes possible. At present our methods are no more accurate or scientific than the flipping of a coin.

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ANTEMORTEM DIAGNOSIS OF TUMORS OF THE HEART.

BY JOSEPH C. DOANE, M.D.,

PROFESSOR OF CLINICAL MEDICINE, TEMPLE UNIVERSITY; ASSOCIATE PROFESSOR OF
MEDICINE, GRADUATE SCHOOL, UNIVERSITY OF PENNSYLVANIA;
VISITING PHYSICIAN, JEWISH HOSPITAL,

AND

ROBERT PRESSMAN, M.D.,

RESIDENT IN MEDICINE, JEWISH HOSPITAL,
PHILADELPHIA, PA.

(From the Medical Service of the Jewish Hospital.)

MALIGNANT metastases of the heart are not particularly rare, but they are discovered in the great majority of cases at the post-mortem table. Our purpose here is briefly to review the literature on the frequency and character of the cardiac tumors most often encountered postmortem and to enumerate that much smaller group of cases which were diagnosed clinically and confirmed by later autopsy.

In 1917 Symmers⁷ reported that in 5155 autopsies performed at the Bellevue Hospital, in 298 cases malignant disease was discovered. Of this number there were 5 instances of metastasis to the myocardium (1.6%). Yater⁸ in 1931 reported 9 cases of tumor of the heart and concluded that malignancies of the heart and pericardium were rare. Burke¹ in 1934 reported 14 cases of metastatic involvement of the heart occurring in 327 patients suffering with malignant disease (4.3%). Lymburner⁴ in the same year reviewed 8550 autopsies performed at the Mayo Clinic. In this number there were 52 secondary tumors of the heart (0.6%), and 4 that were considered primary (0.05%). Helwig² in 1935 found among 1000 autopsies 9 cases in which the heart had been invaded by malignant growth. This same writer states that in 41,000 autopsies compiled from world literature only 98 secondary metastatic malignancies of the heart were discovered. Pollia and Gogol⁵ in 1936 found 29 neoplasms of the heart among 1450 malignant tumors discovered in the performance of 12,000 autopsies (2%). Scott and Garvin⁶ in 1939 reviewed 11,100 consecutive autopsies. Among this number were discovered 1082 cases of malignant tumors, of which 118 were found to have metastasized to the heart or the parietal pericardium (10.9%); 49% of this number were due to the invasion by a carcinoma primary in the bronchus or breast. Lisa, Hirschhorn and Hart³ in 1941 reported 4 tumors of the heart, 1 of which was diagnosed before death.

Because of a growing understanding of the symptoms produced by cardiac malignancy there is a steadily increasing number of patients with tumors of the heart, the nature of whose disease is diagnosed antemortem. A search of the literature on this subject reveals that 20 such cases are recorded. These cases are set down below.

Of these 20 cases, 13 were sarcomata and 7 carcinomata. Of the former group, 3 cases were classified as neuroblastoma, melanoblastoma and myeloblastoma, respectively. In 5 instances the primary tumor involved the bronchus or lung, 4 the tissues of the head (ear, cheek, nose and frontal bone), 1 the uterus, 1 the adrenal, 1 the liver, 1 the femur, and 1 the mediastinum. Twice the tumor was thought to be primary in the heart. Twice the location of the source of the metastasis was not stated. In these 20 cases it is interesting to note that the right auricle alone was very frequently the site of the malignancy (9 cases). Whenever the right heart is involved, the interventricular septum is quite likely to share in the process and the conduction system of the heart then is apt to be embarrassed (9 cases). The left ventricle in this series was involved in 7 instances, in 2 of which the malignant process had extended from the right heart through the interventricular wall to largely affect the mitral valve.

The superior vena cava was invaded and partially obstructed in 3 instances and the pulmonary artery in 1. The pericardium shared in the process in 9 cases.

The clinical pictures presented by a patient suffering with a heart tumor as suggested by Yater fall into two groups. In one, these symptoms but little suggest the true nature of the changes present. Such patients are prone to exhibit signs of sudden and unexplained temporary cardiac failure of a congestive nature. Again the picture is that which suggests a subacute bacterial endocarditis; or finally the patient may experience a sudden and unexpected death.

In the second group, the signs and symptoms point more definitely to the existence of a cardiac new growth. Various abnormalities of cardiac rhythm are commonly met, such as auricular fibrillation, some degree or variety of block, extrasystoles, or paroxysmal tachycardia. Again congestive heart failure developing without apparent cause in a patient hitherto suffering with carcinoma or a rather quickly forming pericardial effusion often of a hemorrhagic nature may occur. Perhaps the most suggestive finding is a fixation of the right border of the heart as shown by the fluoroscope. As has been hitherto remarked, a patient known to be suffering with a malignancy anywhere, but particularly in the adrenals, bronchi, lungs or bones, who develops paroxysmal auricular tachycardia, fibrillation or flutter, a bundle branch or any degree of A-V block or an Adams-Stokes syndrome should be diagnosed as having cardiac malignancy when no other explanation such as the existence of rheumatic or arteriosclerotic heart disease, toxic states or a history of an old coronary infarction is present. As to the electrocardiographic findings present, Barnes believes that the most helpful information is thus secured when the neoplasm involves the ventricles. Nevertheless, as in the case to be reported, conduction defects are noted very frequently when the auricles, especially the right, are invaded.

TABLE 1.—CARDIAC TUMORS DIAGNOSED CLINICALLY AND CONFIRMED POSTMORTEM.

No.	Author.	Journal.	Sex.	Race.	Age.	Primary site.	Metastatic involvement.
1	O. A. Rösler	Zentralbl. f. Herz. u. Gefäßskr., 16, 261, 1924	M	W	47	Sarcoma, left cheek	Interventricular septum and right auricle.
2	A. P. Zenansky, Jr.	Am. J. Med. Sci., 175, 489, 1928	Spindle cell sarcoma, epicardium	Epicardium.
3	A. M. Fishberg	Am. J. Med. Sci., 180, 629, 1930	M	..	69	Carcinoma, rt. main bronchus	Post. surf., right and left auricle.
4	A. M. Fishberg	Am. J. Med. Sci., 180, 629, 1930	M	..	64	Carcinoma, rt. main bronchus	Post. wall, right aur.
5	A. M. Fishberg	Am. J. Med. Sci., 180, 629, 1930	M	..	65	Reticulum cell sarcoma	Post. and lateral wall, rt. aur.; sl. infltr. left vent.
6	F. A. Williams and S. Amberg	Med. Clin. North America, 13, 1307, 1930	F	..	8	Ewing sarcoma, left femur	Rt. vent. in entirety, except. rt. ant. portion of conus.
7	L. Popp	Fortschr. a. d. Gebd. Röntgenstrahler, 46, 23, 1932	M	W	33	Fibrosarcoma	Right auricle.
8	A. R. Barnes, D. C. Beaver and A. M. Shell	Am. Heart J., 9, 480, 1934	F	..	62	Rhabdomyosarcoma, heart	Rt. aur. diffusely involved; nodular involv. rt. vent.; lt. aur. only at interior, septum; pericard. (metast.), infiltration, pericardium.
9	B. R. Heninger	Ann. Int. Med., 7, 1359, 1934	M	W	51	Carcinoma, right lung	lt. aur., auric-ventr. septum and lt. ventr. halfway to apex.
10	S. A. Shelburne	Texas State J. Med., 31, 343, 1935; Ann. Int. Med., 9, 340, 1935	M	Negro	24	Sarcoma, prob. primary in peripheral nerve	
11	M. A. Schmitker and O. T. Bailey	Jour. Am. Med. Assn., 108, 1787, 1937	M	W	64	Bronchogenic carcinoma, rt. primary bronchus	Rt. aur., epicardium; mouth of sup. vena cava involved.
12	J. C. Doane and L. Solis-Cohen	Jour. Am. Med. Assn., 109, 578, 1937	M	W	62	Neuroblastoma, adrenal	Rt. and lt. aur.; inter-aur. septum; also sup. vena cava partial. occluded.
13	D. S. Smith	Jour. Am. Med. Assn., 109, 1192, 1937	F	W	31	Amelanotic melanoblastoma, car	Infiltr., pericard.; neoplastic polypoid thrombi on mitral valve.
14	D. S. Smith	Jour. Am. Med. Assn., 109, 1192, 1937	F	W	25	Spindle cell sarcoma, liver	Metast. involv. rt. aur.; intraventr. septum and about pulm. artery.
15	R. W. Scott and C. F. Garvin	Ann. Heart J., 17, 431, 1939	Carcinoma, bronchus	Heart and pericardium extensively involved.
16	J. C. Hsiung, C. Z. Szutu, C. K. Hsieh, V. T. Lieu	Chinese Med. J., 57, 1, 1940	M	Chinese	58	Reticular cell sarcoma, nose	Gross involv. lt. ventr.; microscopic involv.; rt. and lt. ventr. and inter-ventr. septum; sl. infiltr., aur.
17*	S. A. Shelburne and H. S. Aroson	Ann. Int. Med., 14, 728, 1940	M	W	28	Myeloblastoma, frontal bone	Heart (septum) and pericardium.
18	J. R. Liso, L. Hirschhorn and C. A. Hart	Arch. Int. Med., 67, 91, 1941	F	W	17	Lymphosarcoma, upper retroperitoneal and mediastinal lymph nodes	Pericard., myocard. and interior wall invaded; large masses in ventricles.
19	J. R. Reuling and L. Razinsky	Am. Heart J., 21, 470, 1941	M	W	63	Bronchogenic carcinoma	Pericard., myocard., left ventr. and interventr. wall site of nodular areas; bundle of His and bundle branches destroyed.
20	J. C. Doane and R. S. Pressman	Ann. J. Med. Sci., 203, 520, 1942	F	W	38	Adeno-angiothoma, cervix	Pericard. and rt. aur. with occlusion, sup. vena cava.

* This case not autopsied but tissue obtained from original site; pericardial fluid contained cells identical with those of the original tumor (S. B. Wolbach) and patient developed heart block relieved by irradiation to heart. * Patient subsequently died with the clinical picture of mediastinal tumor.

When and if the ventricles are invaded without conduction interference the electrocardiographic picture may be mistaken for that of an ancient coronary infarction. One of us (J. C. D.) has reported a case in which attention was directed to the possibility of the existence of a cardiac malignancy, even though the presence of a primary lesion was unexpected, on account of the fixation under fluoroscopic examination of the right border of the heart. The occurrence of Adams-Stokes syndrome is not frequent. When such a picture is encountered, however, especially if such attacks are repeated, and more particularly if a more or less distantly located malignancy exists, a cardiac metastasis should certainly be considered. We now wish to record a case, the twentieth we believe in the literature, in which a cardiac malignancy was diagnosed before death and its presence later confirmed by autopsy.

Case Report. E. J. D., female, aged 32, was first admitted to the hospital on July 20, 1932, at which time a perineal repair with cervical dilatation and resection of tissue for biopsy were performed. Histologically, no evidence of malignancy was discovered at this time.

On October 27, 1938, the patient was again admitted to the hospital with a history of a uterine hemorrhage occurring at intervals during the past 3 months. On vaginal examination, the cervix was found to be nodular and friable and bled easily on palpation. A cervical biopsy was reported as adenocarcinoma with infiltration of the endometrium.

On November 9, 1938, under ether anesthesia, a hysterectomy was performed by the abdominal route. The patient then received a series of treatments by deep Roentgen ray therapy, in all 875 r being given. She was discharged from the hospital on November 24, 1938.

On April 12, 1941, this patient was again admitted to the hospital complaining of increasing cough and breathlessness and swelling of the neck and breasts. About 8 months before admission a bilateral swelling of the neck was first noticed. This was then identified as an adenopathy of both the superficial and deep cervical chains. The patient was now very orthopneic, her face being swollen and cyanotic. Her neck exhibited the typical "doll's neck" distribution of fat.

The skin was edematous over most of the upper trunk, the breasts particularly being doughy and cyanotic. Greatly dilated veins were observed over most of the anterior chest, especially below the clavicle on the right side. The right arm was greatly swollen while the left arm was relatively free of edema. Over both bases, below the eighth rib, there was flatness on percussion and breath sounds here were moderately suppressed. The liver and spleen were not palpable. There was no edema of the lower extremities.

The patient soon was unable to breathe with any ease unless the body was flexed at the waist. The skin surface of the chest became more deeply cyanosed through which engorged veins stood out like bluish cords. The heart though difficult to outline seemed enlarged both to the right and left. The sounds were of poor quality. Premature contractions were frequent. The magnesium sulphate and ether tines on the left side were 25 and 18 seconds respectively. The venous pressure was 35 mm. blood in the left arm, the right arm being too edematous to permit the performance of this test.

On April 19, 1941, 1200 and 1300 cc. of a yellow, turbid fluid were withdrawn from the right and left pleural sacs respectively. A cell block of chest fluid was diagnosed as metastatic carcinoma.

An electrocardiographic examination on April 16, 1941, showed sino-auricular block.

Based on the above history and the following physical findings, a diagnosis of malignant metastasis to the superior mediastinum involving the vena cava superior, the right heart, the pleura, the cervical lymph glands was made.

- (a) Evidence of obstruction of the return flow of blood from the head and upper chest (superior vena cava).
- (b) Interference with the conduction system of the heart (sino-auricular block).
- (c) Signs of metastasis to the pleura.

The patient died on April 22, 1941. Autopsy revealed metastasis to the skin of the neck and upper chest (carcinoma *en cuirasse*), the cervical lymph nodes, the superior vena cava producing almost complete obstruction, the pericardium, and the roof of the right auricle. The right ovary and right adrenal showed carcinomatous infiltration.

Comment. That the patient was afflicted with a malignant uterine tumor was known almost 3 years prior to her death. But the picture of a venous obstruction became most prominent upon her last admission to the hospital. The occluding lesion was anatomically located antemortem at a point where the superior vena cava and the right and left azygos veins approach each other, or just at the auricular junction with the superior vena cava. This was indicated by the greatly swollen neck and face and the existence at the same time of greatly distended veins over the anterior chest on the right side descending to the level of the fifth rib. A fixation of the right border of the heart was not noted because only the right auricle was invaded at its uppermost point. The sino-auricular block was very strong evidence that the cause of the venous obstruction was a metastatic invasion of the cardiac auricle especially at the point of entrance of the superior vena cava.

Summary. 1. A case of malignant metastasis to the heart was presented.

2. The 20 cases of heart malignancy which we were able to discover in the literature which had been diagnosed antemortem and confirmed at autopsy were enumerated.

3. The signs and symptoms which indicate the presence of a malignant invasion of the heart were discussed.

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CONDITIONED REFLEX THERAPY OF ALCOHOLIC ADDICTION.

V. FOLLOW-UP REPORT OF 1042 CASES.

BY WALTER L. VOEGTLIN, M.D.,
RESEARCH DIRECTOR, SHADEL SANITARIUM,

FREDERICK LEMERE, M.D.,
CONSULTING PSYCHIATRIST, SHADEL SANITARIUM,

WILLIAM R. BROZ, M.D.,
MEDICAL DIRECTOR, SHADEL SANITARIUM,

AND

PAUL O'HOLLAREN, M.D.,
ASSOCIATE MEDICAL DIRECTOR, SHADEL SANITARIUM,
SEATTLE, WASH.

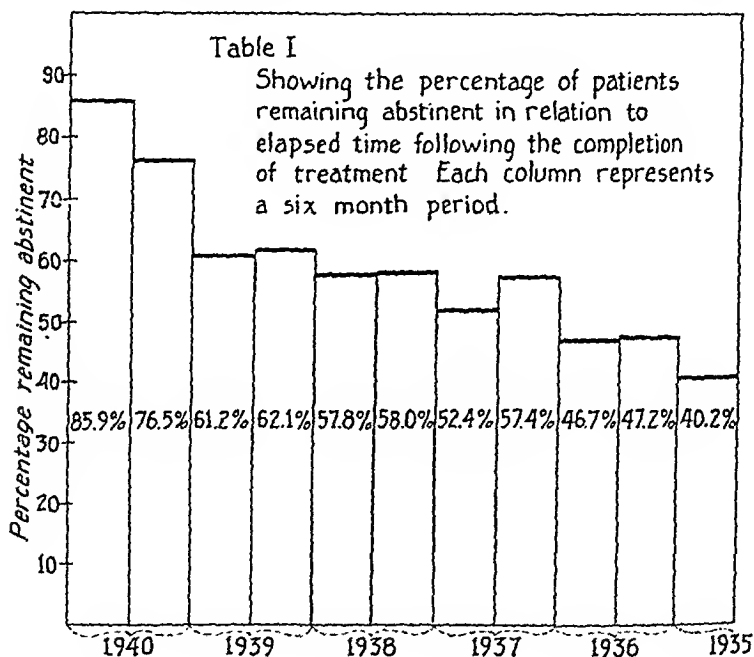
(From the Shadel Sanitarium for the Treatment of Chronic Alcoholism.)

THE method and a preliminary survey of the results obtained in the treatment of 685 cases of alcoholism by a conditioning procedure have been published.¹ A follow-up report is made at this time in order to present additional data covering a larger series of 1042 cases over a somewhat longer observation period of 5½ years.

Results. The summary of data shown in Table 1 includes only those patients known to be living in a conventional environment and whose exact status as regards the drinking of alcoholic beverages has been determined either by direct contact or through other reliable channels. It should be mentioned that this series includes only the results of the original treatment. Patients who have relapsed following the initial treatment are classed as failures, even though some were subsequently retreated and are not drinking at this time. The term "abstinence" as used in the presentation of these data indicates that the patient has refrained completely from alcoholic imbibition of any kind or amount from the time of treatment to the present. The term "relapse" indicates that the patient had indulged in alcoholic drink to some degree even though his relapse was not followed by return to a habitual type of drinking in all cases. A few cases who attempted to drink out of curiosity and were prevented because of the conditioned reflex that had been established, and who have remained abstinent since, are classed as abstinent. It may be seen that the data are presented by 6-month periods which include all the patients treated during that particular period.

Of the total series of 1042 cases, it was found that the exact status of 168 patients was unknown on December 31, 1940, the date on which the survey was based. Forty-three patients of the series had died and 4 had been confined to mental institutions subsequent to the completion of treatment. The remaining 827 patients were found to have shown 532 cases of abstinence (58.6%) and 295

relapses (41.4%). If the data are considered from the standpoint of elapsed time following treatment, it is seen that among the 170 patients treated during the most recent 6-month period (the last half of 1940) there are 85.9% abstinent and 14.1% who relapsed. Of 115 cases treated during the first half of 1940, 76.5% remain abstinent and 23.5% have relapsed. During the last half of 1939, 85 patients were treated, of whom 61.2% remain abstinent while 38.8% have relapsed. Seventy-seven patients were treated during the first half of the same year and 62.1% of these cases remain abstinent. Abstinence is found in 57.8% of the 59 cases treated during the last half of 1938 and 58% of the 62 patients treated dur-



ing the first half of the same year. In 1937, 63 cases were treated during the latter half of the year and 52.4% of these patients remain abstinent, as did 57.4% of the 54 patients treated during the first half of the same year. Data concerning the 1936 cases show 46.7% abstinent among 45 cases for the last half of the year. Among 44 patients treated during the last half of 1935, there is found to be 40.2% of abstinence at this time. The last-mentioned group consists of the oldest of the entire series from the standpoint of elapsed time since the original treatment.

It is interesting to note in passing that of the original series of 1042 cases, there have been 43 deaths since treatment had been completed. This is considerably higher than the death rate for a

similar age group of the population at large. Of the 43 deaths listed, the cause was unknown in 19 instances. Twelve met death through violent or accidental means. Two cases died of pneumonia, 1 of influenza, 3 of heart disease and 1 died postoperatively. There were 2 suicides. Three deaths were considered to be of the result of treatment, giving a mortality of 0.28% for the series. Of the last-mentioned deaths, 2 died of a previously unsuspected coronary disease and 1 of congestive heart failure. Two patients expired during the delirium tremens first appearing several days after treatment had been instituted, and these deaths were considered as not being the result of treatment.

Only 4 cases in the entire series have been confined to mental institutions following treatment. This fact would seem to indicate on the whole a rather satisfactory mental adjustment of the patient to a life of sobriety following treatment.

Discussion. In the original publication of this method, an arbitrary criterion of cure was defined as total abstinence from alcohol of all kinds for a period of 4 years following completion of treatment. A cure expectancy of about 60% was postulated on the basis of the statistical evidence available at that time. It is now possible to present definite information concerning the percentage of cures obtained by this method according to the above criterion for it should be noted that all of the 142 cases treated prior to January 1, 1937, have been observed for from 4 to 5 years since treatment was given. Examination for the data concerned with this particular group reveals that 78 patients have relapsed and 64 have remained abstinent. It may thus be stated unequivocally that on the basis of 142 cases observed for a period of from 4 to 5½ years, 44.7% were cured according to the above criterion. It is felt, however, that this figure represents a rather unfair picture of the results actually obtained by this method for the following reasons: (1) The cases available for study at this time who were treated 4 years ago, or longer, are those who were treated in a more or less experimental fashion before numerous technical minutiae were appreciated and developed and as a result numerous errors of technique were committed. (2) Patients who died prior to the completion of the fourth year of abstinence following treatment cannot be classed as cured, even though they had remained abstinent up to the time of their death. It may thus be appreciated that a patient who relapses immediately becomes a statistical liability regardless of whether he dies or not, whereas a patient who remains abstinent but dies before the criterion of 4 years of abstinence is fulfilled may at best be classed as an unknown result. (3) No credit is here assumed in those cases who relapsed following the original treatment but who are now abstinent following retreatment. It should be emphasized that the 44.7% of cures claimed relates only

to the results following the original treatment and does not include any benefit derived from subsequent retreatment. (4) A recently developed reinforcement technique² which shows promise of markedly enhancing the percentage of cures by this method, was not practised on any member of this group. (5) It should be noted that the consideration of available material does not conform to the criterion of cure on the basis of only 4 years of observation, for some members of the group report have been observed for as long as 5½ years. While the actual percentage of cure would have been somewhat higher if the survey had been terminated at the end of the fourth year in all cases, the figures as presented show that the possibility of relapse cannot be neglected even after a patient has completed the fourth year of abstinence following therapy. As has been mentioned by others, there is probably no time limit for potential relapse.

Compared to the entire series, the 142 cases available for a 4-year survey are too few to form the basis of an absolute conclusion as yet.

While the actual figure for cure is somewhat less than was originally postulated, it is far from discouraging when compared to the figures submitted by others using other methods of treatment.* In view of the preceding discussion, it may be seen that the figure of 44.7% of cures following the conditioned reflex therapy is the minimum that may be expected providing a proper treatment technique is developed. Any change in this figure should be for the better as the method is studied further and improved. It should not be necessary to point out in addition the economic advantage to the patient of a prolonged period of sobriety following treatment although eventually he may relapse and be classified as a failure for statistical purposes.

Summary. 1. A series of 1042 patients suffering from chronic alcoholic addiction who were treated by the conditioned reflex method is reported. Of the total series, it has been found that 58.6% of the cases are abstinent at the present time and that 41.4% have relapsed.

2. In 142 patients who had been observed for 4 years or longer following the completion of treatment, it was found that 44.7% had remained abstinent to the present time and 55.3% had relapsed. This group of patients satisfy the original criterion which requires 4 years of abstinence following the completion of treatment before a cure may be assumed.

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CLINICAL STUDIES WITH THE AID OF RADIOPHOSPHORUS.

II. THE RETENTION OF RADIOPHOSPHORUS BY TISSUES OF PATIENTS DEAD OF LEUKEMIA.*

BY L. A. ERF, M.D.,

WILLIAM R. KENAN, JR., FELLOW AND RESEARCH ASSOCIATE, CROCKER RADIATION LABORATORY; CLINICAL INSTRUCTOR IN MEDICINE, UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL, BERKELEY, CALIF.

THE purpose of this paper is to present the concentrations of radiophosphorus (P^{32}) present in various tissues of 32 patients dead of leukemia,¹ 1 of neuroblastoma and 1 of chloroma. (The blood findings of the latter 2 presented myeloid and monocytoid leukemoid reactions respectively.)

Methods and Materials. The radiophosphorus was produced by the Berkeley cyclotron.² Some of the patients had received single doses of radiophosphorus before death but the majority had received multiple doses. None of the patients had been embalmed. From none of the small pieces (5 to 20 gm.) of tissue removed was the contained blood washed out. The pieces of tissues were weighed, placed in crucibles, ashed at 400° C. and assayed for radioactivity by use of an electrometer.

Results. The results are listed in the accompanying table and are expressed in microcuries per gram of wet weight of tissue assayed. Each determination was corrected for the rate of decay of radiophosphorus (the half-life of which is 14.3 days) to the date of death. Two qualifications of the results must be mentioned: The majority of the patients were in the terminal stages of their disease processes and they received "therapeutic" and not "tracer" doses of radiophosphorus. Both of these factors would alter deductions drawn about phosphorus metabolism of tissues.

Discussion. Because of innumerable variations, such as (a) age, weight, basal metabolic rate and diet of the patients; (b) differences in the types of leukemic processes of the patients; and (c) differences in the amounts and the routes of administration of radiophosphorus, for which corrections were not made, few comparisons of findings are possible, although a few generalizations can be made. Too, it is well known that organs are not uniform in structure or function, and therefore it must be pointed out that the figures of the table are frequently averages of aliquot samples.†

* This work was aided by a grant from the National Advisory Cancer Council.

† For example, in Case 99, the average retention of radiophosphorus of three different pieces of sternum (0.0852, 0.0813 and 0.0940) was 0.0868 $\mu/\text{gm.}$; of two different pieces of kidney (left kidney, 0.151, and right kidney, 0.136), 0.143 $\mu/\text{gm.}$; of two different pieces of spleen (0.0881 and 0.0855), 0.0868 $\mu/\text{gm.}$; of two different pieces of lung (left lung, 0.0392, and right lung, 0.0663), 0.0527 $\mu/\text{gm.}$; and of five pieces of chloromatous tumor (retrobulbar tumor, 0.122; peri-adrenal tumor, 0.149; peripancratic tumor, 0.156; mediastinal tumor, 0.146; and tumor about urinary bladder, 0.125), 0.139 $\mu/\text{gm.}$

TABLE 1.—ASSAYS OF RADIO-
(Expressed in microcuries)

Name and Case No.		Sex and age.	Total millicuries of P ₃₂ administered, and inclusive dates of treatment. O-oral. I.V.—intravenous.	Millicuries P ₃₂ given orally (except 31, 55, 77 and 99) at last administration.	Date of death.	Interval in days between last dose of P ₃₂ and death.	Marrow: Femur—dia.—fd. Femur—spl.—fe. Sternal—a. Tibia—dia.—fd. Vertebra—v.	Bone with marrow.			Lymph nodes, mesenteric: (unless marked) Axillary—a. Bronchial—b. Iliac—i. Spleen—s.	Spleen.	Liver (gall bladder—c).
								Sternum.	Rib.	Vertebra.			
I. MYELOID													
ACUTE.	Far	6	M40	4-28 to 6-30-40 24.11	6.75	7-8-40	8		.174			.230 b—.250	.197 .209
	Ric	10	M67	1-16 to 1-17-40 14.2	7.2	1-17-40	1	s—.486	.317	.342		.320 a—.325	.366 .363
	Wel*	12	F40	7-2 to 7-30-38 5.96	1.19	7-31-38	1						.012 .024
CHRONIC.	Bra†	16	F21	7-20-38 to 1-3-40 46.65	8.1	1-6-40	3	{ s—.068 f—.059	.038	.022		.058	.056 .051
	Cur	18	F18	9-8 to 9-16-39 14.77	4.82	9-21-39	5		.163	.200			.195 .204
	Ebe	19	M39	1-24 to 9-9-39 60.0	3.9	9-15-39	6		.194			.192	.160 .188
	Her	24	M60	12-9 to 12-24-39 21.26	8.2	1-5-40	12	s—.069 f—.072	.059	.096		.050	.067 .066
	Mor	36	F38	9-21-38 to 9-10-39 60.22	4.08	10-19-39	39		.018	.017			.010 .017
	Pac	39	M33	8-4 to 8-6-39 10.32	5.00	8-11-39	5	s—.092	.068	.053			.087 .101
	Rov*	41	M52	2-1 to 8-29-38 90.72	4.65	9-28-38	30	f—.010	.009	.004	.007	.003	.001 .003
	Sml J§	43	M33	5-31-39 to 4-22-40 78.55	10.00	5-11-40	19					.030	.039 .040
	Thom	46	M65	10-18-39 to 2-25-40 28.7	14.8	3-23-40	27	f—.234			.307	.074	.136 .375
	Wat	48	M42	3-17 to 6-25-39 40.47	4.7	7-12-39	17	s—.051	.031		.032		.046 .042
II. MONOCYTOID													
ACUTE.	Agn	92	M40	2-21 to 2-22-39 6.26	3.38	3-6-39	15	fd—.008	.024	.018		.026	.033 .026
	Mac*	93	F24	1-13 to 2-18-38 23.24	9.57	2-24-38	6	s—.161	.162	.107	.117	.105	.149 .131
III. LEUKEMOID													
	Rich	96	M 1	11-17 to 11-29-39 8.3	5.3	12-8-39	9		.258	.415	.328	.129 i—.093	.0845 .115
	Ave	99	M11	1-2-41 to 3-8-41 1.7 (a) 14.08 (i.v.)	1.08 (i.v.)	3-27-41	19		.086			.154	.086 .131

* Previously published.

** Corrected for decay to date of death.

† At time of administration patient was moribund; leukopenic myeloid leukemia.

§ Nodes—not involved.

ACTIVITY** OF AUTOPSIED TISSUES.
per gram wet weight.)

Kidney (urinary bladder—b).																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																									
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LEUKEMIA.

	.097	.120		.142				a— .142	f— .013 s— .022	
.305	.182	.157	a— .058	.640	240	.665	.253	p— 171	tc— .172	f— .030 s— .092
.029			a— .022			.029		a— .028		f— .007
.045		.031	a— .013 d— .017 u— .025		.084	.038	.044	a— .048 b— .002 o— .009	p— .038	s— .009
.113		.125	a— .095	.098	.125		.101	p— 125		
.115	.113	.079	a— .068	.014	.115		.07	p— 106		
.039	.036	.037		.028	.031	.037	.077	a— .045 p— .054	tc— .029	s— .012
.011	.013	.013	a— .011 u— .009	.0076	.010		.009	a— .012 o— .009	p— .022	f— .002 s— .003
.043	.039	.024	a— .015							cr— .0094
.002			a— .003							
.028	.023	.023	a— .013	.004	.0106	.003				
.132 b— .049	.113	.088 a— .035	a— .061	.116	.088	.054	.041	a— 138 p— 176	pr— .040 tc— .078 th— .049	f— .014 s— .017
.028			a— .022			.029		a— .028		f— .007

LEUKEMIA.

.019	.019		.011			.010		a— .013	cr— .0038 cb— .0041 f— .0007 c— .0027	fd— .023
.091	.083						.055	a— .078 o— .062	f— .059	c— .005 to— .035

REACTIONS.

.087 b— .039	.072	.072		.053		.0945		p— .097 tc— .059	th— .103 ty— .091	cr— .025 s— .0165 f— .0136	tu— .109
.143	.052					a— 127 infil- tra- ted		a— .121 p— .156 infiltrated	ty— .0273	cr— .0302 cb— .0568 c— .0528	tu— 139

TABLE 1.—ASSAYS OF RADIO-
(Expressed in microcuries)

Acute.

Chronic.

Name and Case No.	Sex and age.	Total millicuries of P ₃₂ administered, and inclusive dates of treatment. O-oral. I.V.—intravenous.	Millicuries P ₃₂ given orally (except 51, 55, 77 and 99) at last administration.	Date of death.	Interval in days between last dose of P ₃₂ and death.	Marrow: Femur-dia.—fd. Femur-epi.—fe. Sternal—a. Tibia-dia.—td. Vertebral—v.	Bone with marrow	Lymph nodes, mesenteric: (unless marked) Axillary—a. Bronchial—b. Iliac—i. Spleen—s.	Spleen.	Liver (gall bladder—g).		
							Sternum.	Rib.	Vertebrae.			
Ande 51	F 4	2-13 to 2-17-41 2.0	1.00 (i.v.)	2-28-41	11		.0880	.0676	.0690	b—.0587	.0757	.074
Andr 52	F 1	9-15-40 1.00	1.00	9-18-40	3		.0636			.0596	.0710	.1115
Bel 53	M37	7-31 to 8-26-39 20.35	6.95	9-1-39	6	s—.141	.126	.141		.141	.157	.143
Bri 55	F 8	12-17-40 1.9	1.9 (i.v.)	1-3-41	17		.166			.1340 a—.0983	.120	.0735
Gre 58	M45	4-18 to 5-15-40 19.65	2.5	5-19-40	4		.108			.544	.215	.499
Rog E 62	F53	9-15-40 6.6	6.6	9-18-40	3	v—.0884	.0797	.0375		.0663	.0897	.125
Rog M 63	F52	3-4 to 4-12-40 20.33	3.0	5-27-40	45		.0069	.0093	.0063		.0069	.0079
Smi K* 64	F24	12-14-37 to 2-24-38 44.1	6.65	2-26-38	2	s—.338	.275	.210		.318 a—.318	.274	.365
Tui 65	F27	7-25-40 4.0	4.0	8-13-40	20				.0043	a—.0199	.022	.021
Wel 66	M30	6-25 to 6-28-40 9.1	4.1	7-5-40	7					.068 b—.045	.024	.025
Bea 68	M51	9-23-40 5.1	5.1	9-29-40	6			.031		.0203	.047	.050
Chi 70	M69	1-13 to 3-25-40 28.6	15.0	5-29-40	65		.254		.312	b—.007	.0032	.0037
Lea† 77	F61	11-19 to 12-15-40 5.2	2.6 (i.v.)	12-24-40	9			.0378		.0343	.0319 g—.0154	.0378 g—.0154
Sap 84	M48	1-20 to 4-3-40 41.07	6.0	5-5-40	32	s—.029	.068	.038	.042	.032 i—.038	.0159	.0403
Sch 85	M54	10-20-40 20.0	20.0	11-8-40	19	fd—.0249 fe—.0265 td—.0613	.1035	.1438	.0727	a—.0549 b—.0539	.0388 g—.0183	.0669 g—.0183
Tay 87	M49	11-9-39 to 4-9-40 38.62	8.65	5-11-40	23			.0113	.0282	.0162	.0159	.0178
Vol 90	F74	3-17 to 4-6-39 12.24	1.19	5-22-39	46		.003	.0017		.0047	.0047	.0015

IV. LYMPHOMA

* Previously published.

** Corrected for decay to date of death.

† Congested.

‡ All tissues had been placed in formalin.

ACTIVITY** OF AUTOPSIED TISSUES. (Continued.)
per gram wet weight.)

Kidney (urinary bladder—b).	Lung.	Heart muscle (aorta—a).	Muscle: Abdominal—a. Diaphragm—d. Intercostal—i. Tongue—t. Uterus—u.	Gastro-intestinal tract.				Glandular structures.		
				Stomach (duodenum—d).	Jejunum.	Ileum (appendix—a).	Colon (feces—f).	Adrenal—a. Breast—b. Ovary—o. Pancreas—p. Pituitary—pt. Prostate—pr. Testes—te. Thyroid—th. Thymus—ty.	Cerebrum—cr. Cerebellum—cb. Spinal cord—c. Fat—f. Skin—s. (abdominal).	Cartilage—c. Femur—dia.—fd. Femur—epi.—fe. Gall stone—g. Tooth—to. Tibia—dia.—td. Tibia—epi.—te. Tumor—tu.
.0698 b-.0362	.0547 .0540†	.0582 a-.0143	i—.0327 d—.0369	.0305	.0403		.0375	p— .0820		c—.0110
.0589	.0361									
.123	.075	.085	a—.044	.091	.060			a— 110 p— 113		
.0728	.0685							a— 0591	p—.0615	
		.039								
.0676	.067	.0562	a—.0345	.0345 d-.0489	.1145	.044	.058	a— 0556 p— 0663	f—.007 s—.015	
.0047	.0040	.0060	u—.0030	.0041 d-.0052	.0047	.0045	.0036	a— 0065 o— 0038	f—.0005 s—.0014	
.227	.175	.154	a—.142			.092		a— 236	th—.094	c—.219 to—.052
.014	.016									
.0155	.002	.014		.007	.018	.0118	.0116	a— 101 p—.024		
.0357	.030	.025	a—.0147					p—.0328	f—.0154	
.0024	.0081	.0027		.0013 d-.0018	.0011	.0015	.0024	p— 0058	tc—.0030	s—.0055
.0329	.017									f—.0056
.022 b-.0143	.017† .0141	.0218		.033 d- 015	.0121		.0147	p— 035		c—.007
.0472 b-.0139	.0617	.0485 a-.01765	.0365 d—.0304 t—.0458	.0395 d-.0377	.0355	.031	.0263 f-.044	a—.1237 p— 0831 pt-.0516	pr—.0327 tc— 0485 th—.0351	cr—.01836 cb—.0235 c— 0264 f— 0108 s— 01188
.0086	.01	.0117		.0106	.0069	.0080	.0053	p—.0188		
		.0036	.0029							c—.003

In those patients (as in Cases 41, 70, 84) who had received radiophosphorus many days before death, the concentrations of P^{32} were frequently greatest in the osseous tissues, while in those (as in Cases 10, 39, 64) who had received radiophosphorus just before death, the concentrations of P^{32} were greatest in such tissues as the bone marrow, lymph nodes, spleen and liver. These findings suggest that radiophosphorus is first utilized by the more rapidly metabolizing tissue or those most frequently infiltrated with leukemic cells and that later it finds its way to the bones. Of the tissues that are constantly producing cells, such as skin, ovaries, testes and marrow, in only the latter did radiophosphorus concentrate in significantly large quantities. It can be observed, also, that heart muscle retained P^{32} in greater quantities than did abdominal, diaphragmatic, intercostal, tongue or uterine muscles. The central nervous system retained relatively small concentrations of radiophosphorus. The cerebellum, however, retained more P^{32} than the cerebrum, which may or may not be due to the greater proportion of gray matter in the cerebellum.*

When the *number* of days between the last dose of P^{32} and death, and the *amounts* of the last dose of P^{32} are similar, one can observe that the tissues retained comparable amounts of radiophosphorus regardless of type of leukemia or leukemoid reaction (compare Cases 6, 19, 53 and 96). Using the same criteria, tissues of acute and chronic forms of the same type of leukemia retain comparable amounts of radiophosphorus in some (compare Cases 6 and 19, 63 and 90), but not in all instances. Of 3 cases (Cases 55, 65 and 85), who received single doses of radiophosphorus 17 to 20 days before death, the tissues of the child (Case 55) who received P^{32} intravenously retained more radiophosphorus than those of the other 2 cases which had received orally much larger doses of P^{32} . Among many explanations, this increase in retention may be due to the route of administration of P^{32} , to the acuteness of the leukemic process or to the immaturity of the patient.

In 1 instance (Case 16) the patient was moribund when the P^{32} was administered and the tissues of this case retained relatively small amounts of radiophosphorus.

The results and generalizations are confirmatory of those found previously in mice.^{3,4}

Summary. The amounts of radiophosphorus (following its oral and intravenous administration) retained by various tissues of 32 patients dead of leukemia, are presented. These findings suggest how phosphorus is quantitatively distributed in the tissues of persons dead of leukemia at various intervals of time and under the conditions mentioned after its administration; and demonstrate

* In Case 99 an aliquot portion of the cerebrum contained 0.0302 $\mu\text{gm.}$; but the gray matter of the cerebrum contained 0.0404 $\mu\text{gm.}$ while the white matter contained 0.0188 $\mu\text{gm.}$

that radiophosphorus concentrates in greatest quantities in those tissues which are most frequently infiltrated with leukemic cells.

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AN OBJECTIVE METHOD OF DETERMINING BLOOD VELOCITY (FLUORESCEN METHOD.*)

BY DAVID B. FISHBACK, M.D.,
PATHOLOGIST AND ASSISTANT IN MEDICINE,

SAMUEL A. GUTTMAN, PH.D., M.D.,
HOUSE PHYSICIAN,

AND

EDWIN B. ABRAMSON, M.D.,
ASSISTANT IN MEDICINE, JEWISH HOSPITAL,
PHILADELPHIA, PA.

IN recent years, attention has been directed toward determining the velocity of bloodflow (circulation time) in health and disease. The most satisfactory methods are subjective in nature, that is, the patient states when he feels a certain sensation after the injection of some foreign substance into the blood stream.^{1,3,6,8,13} The unreliability of this procedure is apparent because the observer depends on the patient who may be slow in cerebration, or unable to understand what reaction is to be determined for an end point. Such a method cannot be used in small children, comatose, anesthetized, mentally ill and moribund patients. An objective method of determining circulation time would therefore have certain advantages.

With these factors in mind, various objective methods have been reviewed. These procedures have been either complex or unreliable. They include the following:

In 1829, Hering¹⁰ injected potassium ferrocyanide into the jugular vein of animals. He was able to note how many seconds it took the potassium ferrocyanide to reach the jugular vein on the opposite side by adding perchloride of iron which gave a blue reaction.

In 1912, Bornstein⁵ used carbon dioxide inhalations. This method was supposed to measure the velocity of the blood from the pulmonary capillaries to the respiratory center and was dependent for its end point on the first deep breath.

In 1922, Koch⁹ described an objective method using sodium fluorescein. This method consisted of injecting 1 cc. of a mixture containing fluorescein 2 gm., sodium bicarbonate 4 gm. and distilled

* This study was aided by a grant from the Jewish Hospital Research Fund Philadelphia, Pa.

water 120 gm. Samples of blood were then removed at 5-second intervals and collected in oxalated tubes. The first appearance of the dye in these tubes was then determined.

In 1927, Blumgart and Weiss⁴ described a radium emanation method. Small non-toxic doses of radium emanation were injected into the blood stream and its arrival at various points in the circulation was detected by a sensitive device (Geiger counter) to pick up the emanations as they arrived.

In 1929, Weiss, Robb and Blumgart¹⁴ described a method using histamine. This depends upon the development of an intense flush of the face and neck caused by the arrival of the histamine in the blood vessels in the skin.

In 1930, Lian and Barras¹⁰ used 2 cc. of a 5% solution of fluorescein intravenously in the right arm and withdrew the blood from the vein in the left arm at the end of 5- to 10-second intervals. Their normal circulation time from arm to arm was 30 seconds.

In 1936, Moore and Kinsman¹¹ used an aqueous solution containing 300 mg. of brilliant vital red and injected this into an arm vein. They then collected samples of blood from the femoral artery at stated intervals and determined the amount of dye in the blood samples.

In 1939, Stead and Kunkel¹² and some years prior to this Blumgart and Weiss⁴ described a method using sodium cyanide. They injected 0.2 to 0.4 cc. of a 2% solution of sodium cyanide (4 to 8 mg.) and the time interval for the first deep breath was recorded. This method measures the time interval actually to the carotid sinus and depends on the degree of sensitivity of the sinus for its effect.

In 1940, Berliner² determined the circulation time using 0.5 cc. of a 1% solution of alpha lobelin intravenously. This method, like the cyanide method, is an arm to carotid sinus time, and the end point is dependent on the patient's coughing, or developing a strangling sensation.

It thus becomes apparent that the objective methods described to date are either complex, not entirely reliable, expensive, require unusual technical proficiency or are even dangerous. It was with these factors in mind that one of us (D. B. F.) sought for a simple method, using a dye with a minimum toxicity. Fluorescein solutions (10% and 20%) were found to give the best color reactions. This procedure was employed in rabbits in over 150 experiments, using up to 25 cc., without noting any deleterious effects.

In 1940, Gifford⁷ reported that he used 10 cc. of a 10% solution of sodium fluorescein intravenously in humans as an aid to ophthalmic diagnosis and treatment. He concluded that it was non-toxic and produced no unpleasant symptoms in the patient. This confirmed our previous findings.

Method. The test for circulation time is done as follows: Using sterile precautions, an 18-gauge needle attached to a syringe containing 4 cc. of a

10% or preferably 3 cc. of a 20% sodium fluorescein* solution is inserted into the antecubital vein of the arm. The room is then darkened, and the fluorescein injected rapidly into the vein. The assistant, using a portable ultraviolet source with a Wood's filter, directs the light to one of the eyes of the patient, observing the palpebral conjunctiva. The first appearance of a brilliant yellow color in the lower palpebral conjunctiva is the end point. The end point is sharp, especially if the room is dark. The time elapsed from the moment of injection to the appearance of the dye in the eye is recorded.

Thus, the circulation time from the antecubital vein of the arm to the conjunctiva of the eye is accurately determined.

Results. This circulation time test was done in over 50 patients with supposedly normal hearts or patients with fully compensated cardiac disease. The time varied from 7 to 15.6 seconds.

In another group of patients with cardiac disease undergoing decompensation, the circulation time varied from 16 to 25 seconds. One cardiac case with marked decompensation had a circulation time of 45 seconds.

No untoward reactions occurred in any of the patients.

In 4 patients, when the dye was inadvertently injected outside the vein, there was but very little pain, and no inflammation or sloughing resulted. No treatment was instituted, and the injected material disappeared within a few days.

In another group of cases, magnesium sulphate was used to measure the circulation time within several days prior to the injection of fluorescein. As will be noted in the following table, the results were somewhat similar.

TABLE 1.—COMPARATIVE CIRCULATION TIMES (MAG. SULPHATE-FLUORESCEIN)

Patient.	Sex.	Age.	Diagnosis.	Mag. sulph. (sec.).	Fluorescein (sec.).
L. S.	M.	66	Arteriosclerotic heart disease	13	11.2
H. S.	M.	47	Carcinoma of lung	10	9
F. B.	M.	60	Diabetes mellitus	10	11.2
				12	
N. S.	M.	70	Carcinoma of stomach	10	6.5
				8	
K. S.	M.	30	Constrictive pericarditis	11	11.4
				13	
R. R.	M.	40	Psychoneurosis	14	11.5
				11	
C. M.	M.	67	Arteriosclerotic heart disease, mitral and aortic insufficiency	14	19.6
				17	
M. H.	M.	14	Intestinal allergy	12.6	13
				13	
J. S.	M.	28	Acute rheumatic fever, lues, partial heart block	12	15.2
				11.5	
S. B.	M.	51	Hypertensive heart disease	13.2	16.6

The reason for the slight difference between the circulation times for magnesium sulphate and fluorescein is because they were done on different days and the circulation time may vary from day to day.

* The 20% sodium fluorescein solution in distilled water was filtered with filter paper and autoclaved for 20 minutes.

Two successive readings were usually done with the magnesium sulphate.

To offset the normal variation in the circulation time from day to day, another group of patients received calcium gluconate (5 cc. neocalglucon) and fluorescein (4 cc. 10% sod. fluorescein solution) simultaneously.

TABLE 2.—CIRCULATION TIME—CALCIUM GLUCONATE AND FLUORESCIN SIMULTANEOUSLY

Patient.	Sex.	Age.	Diagnosis.	Ca. glucon. (sec.).	Fluorescein (sec.).
F. W.	M	71	Hypertensive heart disease	22.0	22.0
L. R.	M	55	Encephalitis	14.8	14.8
J. S.	M	79	Carcinoma of stomach 1 month later	26.0 13.0	27.0 13.0
H. S.	M	62	Coronary sclerosis	13.0	13.0
L. G.	M	33	Hyperthyroidism	11.0	15.6
J. G.	M	60	Acute cardiac decompensation	27.0	28.2
M. M.	F	70	Hypertension, pulmonary cyst	13.8	13.8
N. K.	M	11	Gastro-intestinal allergy	12.0	12.0
L. T.	M	57	Lymphoblastoma	17.0	19.6
I. S.	M	69	Peptic ulcer	9.5	11.5
A. G.	M	35	Thyrotoxicosis	10.6	15.0
M. K.	M	52	Lobar pneumonia	12.8	12.8
H. S.	M	55	Carcinoma of rectum	11.6	11.6
C. G.	M	70	Buerger's disease	22.4	22.4
S. L.	M	85	Complete heart block	28.6	28.6
D. Q.	M	67	Diabetes mellitus	19.0	19.0
H. R.	M	60	Gastro-intestinal malignancy	16.0	16.0
W. H.	M	50	Carcinoma of lung	21.0	21.0
M. W.	M	63	Buerger's disease, hypertensive heart disease	24.0	26.6
I. S.	M	70	Duodenal ulcer, hyperthyroidism, carcinoma of urinary bladder	9.5	9.7

In this series of 20 cases, only 2 showed variations of more than 3 seconds between the calcium gluconate and fluorescein circulation times. Both of these were cases of hyperthyroidism. Since the fluorescein method is objective and the calcium gluconate method subjective, it is of interest to have found that they give similar results. However, in those patients who are slow in cerebrating, unconscious, mentally ill, moribund, and so on, calcium gluconate cannot be used. Fluorescein is being used in such cases and a reliable circulation time is being obtained. Patients with malignant tumors who are undergoing general refrigeration are being subjected to the fluorescein circulation time test. These studies will be reported later.

Patient.	Sex.	Age.	Diagnosis.	Refrigeration.	
				Before (sec.).	During (sec.).
N. L.*	M	68	Primary carcinoma of rectum, generalized metastasis.	9.4	17.6

* By courtesy of Dr. Lawrence W. Smith and Dr. Temple Fay.

Summary and Conclusions. 1. A new objective circulation time test has been described, using fluorescein.

2. The data obtained indicate that the method is reasonably simple, not harmful to the patient, and reliable as indicated by comparison with other methods.

3. This method is of particular advantage in determining the blood velocity in small children, comatose, anesthetized, mentally ill and moribund patients.

4. In patients with normal hearts or fully compensated cardiac disease, the circulation time varied from 7 to 15.6 seconds. In another group of patients with cardiac disease undergoing decompensation, the circulation time varied from 16 to 25 seconds, one being 45 seconds.

We wish to thank Miss Annette Spear for her valuable assistance.

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PSYCHONEUROTICS FIVE YEARS LATER.

BY CONSTANCE FRIESS, M.D.,

ASSISTANT ATTENDING PHYSICIAN, NEW YORK HOSPITAL; INSTRUCTOR IN MEDICINE,
CORNELL UNIVERSITY MEDICAL SCHOOL,

AND

MARJORY J. NELSON, M.D.,

ASSISTANT PHYSICIAN TO THE OUT-PATIENT DEPARTMENT, NEW YORK HOSPITAL,
NEW YORK, N. Y.

(From the Department of Medicine, Cornell University Medical School and New York Hospital Medical Out-Patient Department.)

No group of ambulatory patients presents greater difficulty of management than the psychoneurotic group. It comprises a high percentage of all patients, and is peculiarly vulnerable to the multiplicity of doctors and special clinics encountered in a large teaching hospital. The psychoneurotic patient finds himself between a Scylla and Charybdis: on the one side is the physician who either through ignorance or personal prejudice overlooks the important psychobiologic factors, and, searching endlessly for some organic basis for the patient's complaints, increases the latter's insecurity and exhausts his resources. On the other side is the psychiatrically minded, if not psychiatrically trained physician who, because of an

innate sympathy, recognizes early the psychoneurotic elements but fails to discover and evaluate coëxisting organic disease.

A special interest in psychoneurotic patients and their problems in a large out-patient clinic prompted the present study. The investigation concerned itself with the problem as encountered in a general medical clinic and, therefore, many of the patients suffered from coëxisting disease. The careful reëxamination of a group of these patients *after a 5-year interval may achieve more than a mere discovery of previously unrecognized organic disease.* By studying the variability and volatility of the "complaint," the natural course of the untreated illness, the effect of intercurrent diseases, operations, environmental changes and medical and psychiatric treatment, an effort is made to sharpen and clarify our concepts of a hitherto poorly defined disorder. The cost of medical care in this group is also studied in an attempt to devise methods of management less costly both to the patient and to the medical agencies concerned with his care.

A review of the literature reveals an abundance of general, philosophical articles which do little more than urge a greater interest in psychoneurotic patients. Journals of neurology and psychiatry contain many exhaustive studies dealing with special aspects of the neuroses, but few reports^{1,2,4} comparable to the present one are available. This may be due to certain limitations and difficulties which are recognized early in the study, and are worthy of mention at the onset:

1. Data from psychoneurotic patients are notoriously difficult to tabulate, for similar complaints may arise from very different settings.

2. Since most psychoneurotic patients eventually succumb to organic disease, it is not always possible to determine the true origin of their symptoms.

3. It is a formidable task to follow any group of patients not regularly attending a clinic.

Selection of Cases. The records of 3587 consecutive patients seen in the General Medical Clinic of The New York Hospital from September 1, 1932, to January 1, 1934, were reviewed. Those in which a diagnosis of psychoneurosis was made were selected for this study. Any of the following variations in terminology were accepted, whether occurring alone or in conjunction with organic disease: anxiety state, neurasthenia, neurocirculatory asthenia, psychasthenia, hysteria, functional tic, gastric or cardiac neurosis, functional disease, or psychopathic personality. Patients with major psychoses (schizophrenic, manic-depressive, depressive, toxic or degenerative) were discarded, as were those suffering from epilepsy or other organic diseases with a marked personality coloring, such as migraine and Graves' disease.

The group thus selected comprised 498 patients (13.9%) of the

total number of records reviewed. Table 1 shows the number of patients interviewed and examined, the number not examined in whom data was obtained indirectly, either through correspondence or Social Service agencies, the number in institutions for mental diseases, the number dead, and the number lost.

TABLE 1.—ANALYSIS OF MATERIAL.

Interviewed and examined.	Indirect data.	Confined to institutions for mental diseases.	Dead.	Lost.	Total.
177 (35.6%)	69 (13.8%)	9 (1.8%)	14 (2.8%)	229 (46%)	498 (100%)

The task of contacting these patients was laborious, for many had moved a number of times since their last visit to the hospital. This work was done by a social worker, Miss Alice Fahmy, who in the course of the study wrote 1759 letters and made 155 home visits.

Method of Study. A careful history, physical examination, urinalysis, and Wassermann test were done on all patients interviewed. Special laboratory tests were performed when indicated. In eliciting the history particular attention was focused on the following points: 1, complaints offered spontaneously as differentiated from those elicited by questioning; 2, physical illnesses in relation to the environmental setting at the time they occurred; 3, changes in family relations, working conditions, social and economic status; 4, sources of medical care and its cost.

Patients who had been treated in the psychiatric clinic or seen by a psychiatric consultant prior to the follow-up examination were reexamined by a psychiatrist* who was asked to contrast the present psychiatric status with that of 5 years ago, and to give an opinion regarding possible benefits which might have followed earlier or more intensive therapy.

Analysis of Data. *Sex.* Of the 269 patients contacted, 109 (40.5%) were males and 160 (59.5%) were females, a proportion of 1:1.4. The proportion of males to females for all cases in the general medical clinic is 1 to 1.6. There was no disproportion in the sex distribution of the psychoneurotics in this series.

Age. The age distribution was as follows: 16 to 25, 39; 26 to 35, 83; 36 to 45, 81; 46 to 55, 45; 56 to 65, 21; 66 to 75, 0; 45.3% of the group were less than 36 years of age.

Social Status. More than one-half of the patients were married, 110 (59%); 74 (28%) were single; 21 (7%) were widowed; and 15 (6%) were separated or divorced.

Nationality. The New York Hospital is located in the mid-eastern section of New York City and it draws upon a foreign-born population of Germans, Italians, Austrians and Hungarians for a large percentage of its patients. In this study the foreign-born element was not as high (37%) as it is in the general clinic (43%). Two races which form only 13% of the general out-patients, the Russians and Poles, comprised 30% of the cases here studied. There were but 3 negroes in this series.

* Dr. Phyllis Greenacre or Dr. Emeline Hayward.

Religion. The following table shows the religion of the patients studied as contrasted with that of the out-patient department as a whole.

TABLE 2.—RELIGIONS OF CASES ANALYZED.

	Roman Catholic, %	Protestant, %	Hebrew, %	Greek Catholic, %	Unclassi- fied, %
Study group	34	29	28	2	7
Out-patient department	52	28	16	2	2

This supports the common belief that psychoneurotic disorders are more common among the Jews.

Employability. In 1932-1933, 100 (37%) of the patients were regularly employed, 96 (35%) were housewives, 7 (3%) were students and 66 (38 males and 28 females, 25%) were unemployed. Five of the males claimed to be unemployed because of their health; the remainder were unable to find work.

Coexisting Organic Disease. An arbitrary division was made between major and minor organic diseases. Under the classification of major diseases were conditions which might at some time incapacitate the patient or threaten his life; under minor organic diseases are placed the less serious conditions. The defect of such a division is illustrated by two types of cases. Myoma uteri, classified as a minor, has the potentiality of becoming major; whereas acne vulgaris, a minor ailment, may have major effects upon the patient's psychobiological status.

Sixty-seven (25%) of the patients had evidence of major organic disease at the time of their original visit. In only 30 cases (11%), however, were any of the original complaints referable to the major disease diagnosed at this time. One hundred and fifty of the patients (55.8%) had evidence of minor organic disease at the time of their original visit. Of the minor ailments, the commonest were those related to low-grade infections in the nose and throat, problems of nutrition; and pelvic abnormalities. Ninety-nine (37%) had no major or minor organic disease.

Clinics Attended. Only 48 patients (18%) were cared for in one clinic in The New York Hospital Out-Patient Department; 219 patients (81.4%) attended 5 or less clinics and 50 patients (18.6%) attended from 6 to 20 clinics.

On scrutiny it was found that the referral of patients to more than 5 clinics was rarely due to diagnostic difficulties. In most instances it was traceable to the difficult or obnoxious personality of the patient. The facility of the clinic refer system and the absence of incentive for the clinic physician to care for difficult personalities fosters the habit of "passing the buck" in clinic practice. In private practice this is discouraged by financial considerations and the desire to keep the patient satisfied.

Chart 1 shows the ratio of clinics per patient.

Amount of Psychiatric Treatment. One hundred and twenty-nine patients (48%) received psychiatric treatment; 38 of these (14.1% of the whole group) made more than 5 visits to a psychiatrist, and are designated as having had "considerable psychiatric care." This group of 38 patients made 628 visits within a 5-year period, an average of 16.5 visits per patient. The greatest number of psychiatric visits made by any one patient was 110 visits (No. 4071, E. K., who had severe hypertensive cardiovascular disease). Ninety-one patients (33.8%) made less than 5 visits to a psychiatrist and

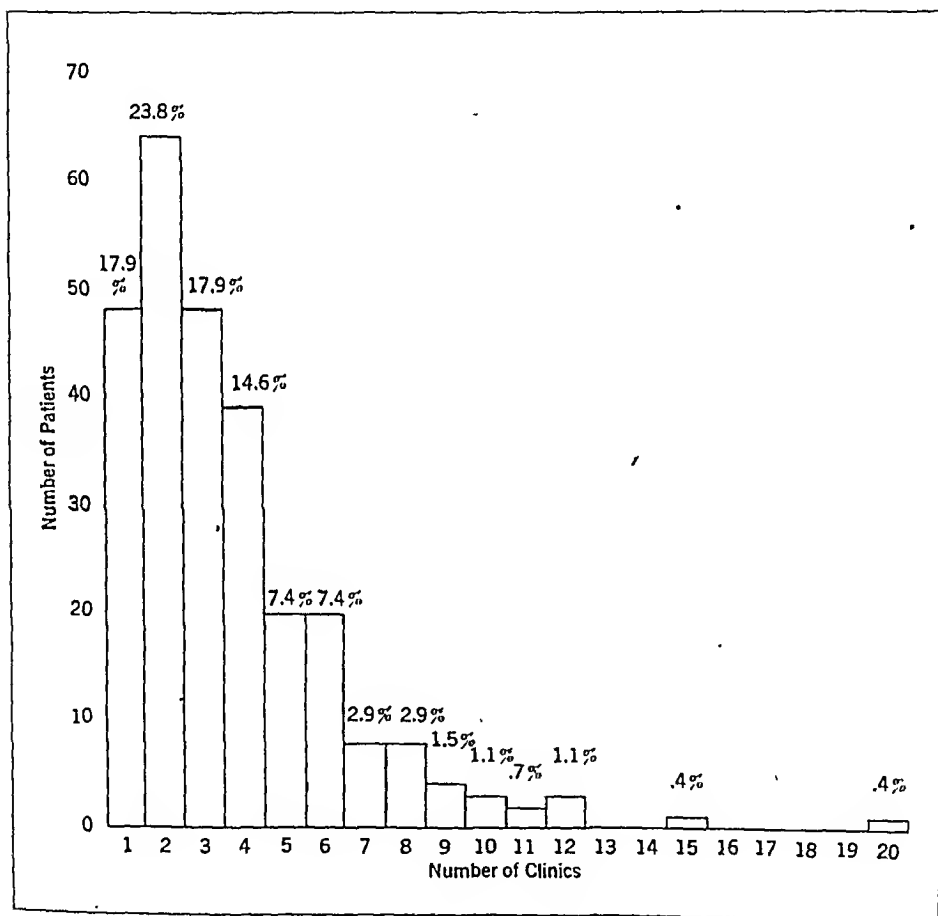


CHART 1.—Ratio of number of clinics per patient.

are designated as having had "some psychiatric care." In this group 91 patients made 168 visits, or an average of 1.8 visit per patient within the 5-year period.

It is important to note that there was no direct ratio between the severity of the neurosis and the amount of psychiatric treatment. A number of patients with stubborn, deep-rooted psychoneuroses were considered by the psychiatrist to be unsuitable for further psychiatric care, whereas others with less severe symptoms were considered amenable to psychotherapy. Although one group is

designated as having had "considerable psychiatric care," the type of psychotherapy carried out in the Out-Patient Clinic is admittedly of a superficial character.

Incidence of Operations. It is commonly believed that neurotic patients are particularly susceptible to the drama of surgical therapy. Almost every clinician has among his patients at least 1 case of "surgical addiction."³ It is with interest, therefore, that the incidence of operations in the group studied is compared with that of a control group of similar age and sex distribution. Accurate surgical histories were obtained from 179 psychoneurotic and 100 control patients.

TABLE 3.—INCIDENCE OF OPERATIONS.

Group.	Operations.			No operations (%)	Total No. of operations.	Operations per person.
	Major (%)	Minor (%)	Major and minor (%)			
179, psychoneurotic patients	15	26	31	28	286	1.6
100 control patients	17	72	11	30	111	1.1
		52				
		70				

Table 3 shows almost identical percentages of operative and non-operative cases in the psychoneurotic and control groups. Further analysis reveals certain differences. The high incidence of minor operations in the control group (42%) is largely due to the tonsillectomies done in childhood. Although the incidence of tonsillectomies in the psychoneurotic group is as great; many more of these had subsequent major procedures (31% as compared with 11%). The number of operations per patient in the neurotic group is persistently higher than in the controls (1.6 to 1.1), due largely to the absence of cases of "surgical addiction" in the latter group. These figures serve to emphasize the fact that the psychoneurotic patient once operated upon is more likely to undergo subsequent procedures than the mentally stable individual.

A correlation between the number of psychiatric interviews and the number of operations during the period of treatment was attempted. Table 4 shows the highest number of operations per patient in the group having the greatest number of psychiatric visits but the difference is not sufficiently striking to draw any conclusions.

TABLE 4.—INCIDENCE OF OPERATIONS DURING PERIOD OF PSYCHOTHERAPY.

Group.	Patients operated upon, %	Total number of operations.	Operations per patient.
5 or more psychiatric visits	19	12	0.38
Less than 5 psychiatric visits	20	17	0.26
No psychiatric visits	16	21	0.25

The Complaint. The patient's complaint was studied in some detail, since it was the focal point about which the illness developed. The complaints were single or multiple, fixed or inconstant.

Original Complaints. The original complaints were grouped under the system or part of the body to which they referred. Muscular spasms (tics) and fears (phobias) were listed separately because of their unique quality. Only 35 patients (13%) had complaints related to one system of the body. The total number of symptoms, therefore, exceeded the total number of patients.

Chart 2 shows the distribution of complaints according to systems of the body. By far the commonest complaints were those related to the nervous system or to the body as a whole. One hundred and fifty-four patients (57.2% of the entire group) complained of ner-

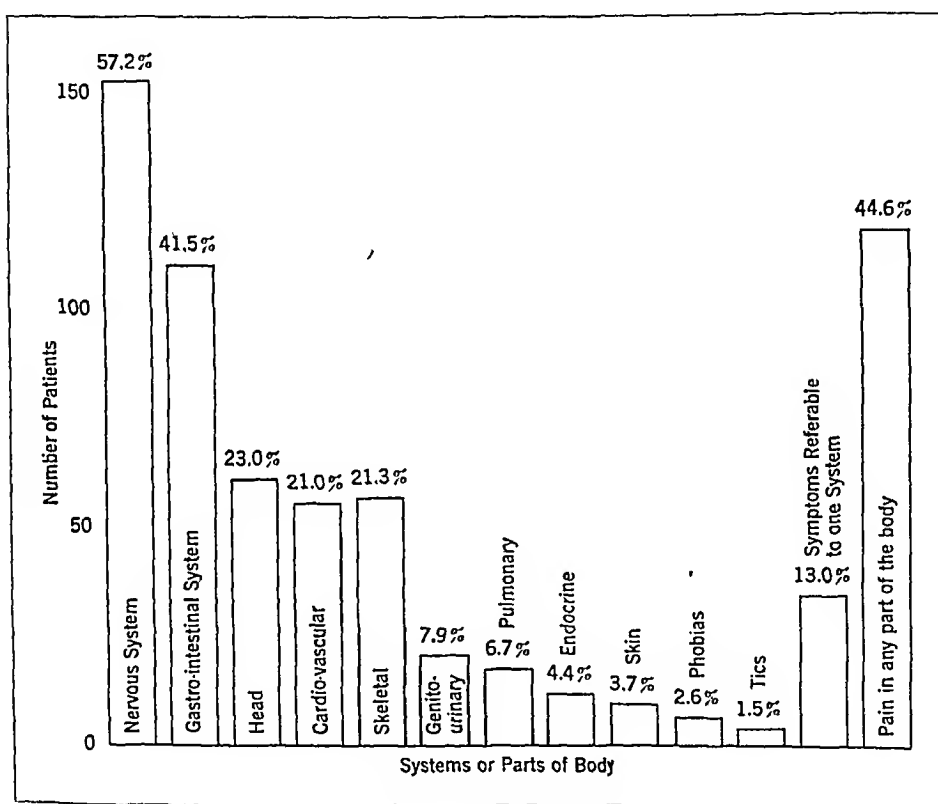


CHART 2.—Symptom chart.

vousness, weakness, fatigue, insomnia, dizziness, irritability, numbness, tremor, sweating, loss of weight, drowsiness, worrisomeness, apprehension, loss of pep, lessened libido or inability to concentrate. These were frequently accompanied by more specific complaints referable to other systems of the body.

The second largest group, consisting of 111 patients (41.5%) was referred to the gastro-intestinal tract. In the order of their frequency the symptoms were abdominal pain, gas (belching, sour eructations, or flatulence), nausea, constipation, vomiting, halitosis, sore tongue, anorexia, difficulty in swallowing, and rectal pain. Nausea and vomiting without abdominal pain, often considered a

neurotic syndrome,⁶ was rare in this group. Nausea occurred more frequently as an isolated symptom. The "mucous colitis" syndrome⁵ occurred in 5 females, but diarrhea was uncommon.

Fifty-six patients had cardiovascular symptoms. Frequently the symptoms could be traced to the patient's overhearing or being told that he had a heart murmur. One woman when running up the stairs of a hospital to visit her daughter was waylaid by a passing nurse who remarked that "your lips look so blue you must be courting a heart attack." On the same day this patient developed pain in the region of the left breast that has persisted for a period of 3 years. Such inadvertent remarks are often misinterpreted by psychoneurotic patients and may be the seeds from which full-fledged neuroses develop.

Pain was the commonest of the cardiovascular complaints. It was rarely substernal but commonly felt over the left chest and under the breast. Only 3 patients had true dyspnea, but many complained of difficulty in breathing deeply or of the necessity for sighing, a characteristic psychoneurotic phenomenon. Two patients with marked hypertension had no cardiovascular symptoms.

Of the 61 patients with head symptoms, 55 complained of headache, two-thirds of them being women. Characteristic of the headache of psychoneurotic origin was its indefinite onset, termination, and localization. Only 2 patients had headaches occurring in well-defined attacks, both of whom were later shown to have typical migraine. In 3 patients the headache was attributed to organic disease (Paget's disease of the bone, central nervous system syphilis and marked hypertensive cardiovascular disease). Other head symptoms included pain in the face, tinnitus and burning of the eyes.

Symptoms referable to the skeletal system occurred in 57 patients. It was more common for the pain to arise in the muscles between the joints than in the joints themselves. In spite of the absence of objective changes, the clinician usually regarded the pain in the skeletal system as due to early arthritis or myositis. In many of these cases there were no objective signs or positive laboratory findings indicative of arthritis even 5 years later at the time of the reexamination. All of these patients had received some treatment for arthritis; 1 had been attending the arthritis clinic for vaccine injections throughout the entire 5 years. It cannot be overemphasized that a diagnosis of arthritis or myositis based alone on the subjective symptom of pain should be regarded with suspicion if supporting evidence is not found after the lapse of a year. It is certainly advisable to avoid use of the term "arthritis" to the patient until confirmatory evidence is found.

Symptoms related to the genito-urinary system were less common than was expected, possibly due to the referral of many such patients directly to the urologic clinic. Twenty-one patients had genito-urinary complaints which were distributed as follows:

	Females.	Males.
Pain over the kidneys	3	2
Pain on urination	4	
Nocturia	1	1
Frequency	2	4
Impotency	2
Penile discharge	1
Vaginal discharge	1	

Nephropexies were done on 2 of these patients without relief.

Seventeen patients had respiratory symptoms. In order of frequency these symptoms were cough, chest pain, frequent upper respiratory infections, hoarseness and sputum. Two of these had bronchial asthma; one severe, the other mild. Three patients with arrested pulmonary tuberculosis had no pulmonary symptoms.

All of the 12 patients with endocrine symptoms were women complaining of hot flushes associated with the menopause. Less specific endocrine symptoms are grouped under other categories. Due to advances in ovarian replacement therapy since 1932, these symptoms can now be partially controlled.

Ten patients with symptoms referable to the skin and lymphatic system complained of urticaria, generalized itching, perineal itching, burning of the skin, swollen glands and loss of hair.

Four patients complained of tics, involving the facial or neck muscles, and 7 patients suffered from phobias. The most common of the phobias was fear of food contamination by dirt or by dangerous objects such as needles. These patients could be classified as obsessive neurotics having ruminative tension states.

The Complaint Five Years Later. Thus far the complaints at the time of admission to the dispensary (1932-33) have been discussed. These complaints are now compared with those present at the time of the follow-up examination 5 years later. Only cases questioned and examined by the authors are reported in this table.

TABLE 5.—SHOWING FIXITY OF COMPLAINTS.

	No. of patients.	Change due to organic disease.	Change due to neurosis.
Complaints the same	116		
Complaints changed:			
Same plus new	29	20	9
All new complaints	22	3	19
No complaints	10	4	6
Total	177	27	34

In the group developing new symptoms in addition to the original complaints (29 patients), 13 are accounted for by women entering the menopause, and 7 others by the development of intercurrent organic disease. In only 9 cases were new symptoms due to an extension of the neurosis.

In 22 patients developing an entirely new set of complaints, only 3 were found to have organic disease pertinent to the new symptoms.

In the complaint-free group, 4 patients were cured when organic disease thought to cause their symptoms was corrected (terminal ileitis, cholecystitis, severe hypochromic anemia and dietary deficiency). The other 6 attributed former complaints to some temporary stress or strain which was subsequently relieved by a change in circumstances.

It is of considerable interest that after a lapse of 5 years, two-thirds of the group questioned (116 patients) had the same complaints as at the original examination. If to these are added the 27 patients whose new complaints were due to organic disease, we find that only 34 patients of the group of 177 (19%) changed the nature of their neurotic complaints. This fixity of the complaint is but one manifestation of the basic changelessness of the psychoneurotic patient, and probably represents his most outstanding characteristic.

Results. The patient's status after 5 years is designated in one of the following ways:

1. *Original Diagnosis of Psychoneurosis Incorrect.* In this group other causes for the patient's symptoms were found and there was no evidence of a psychoneurosis at the time of the follow-up examination.

2. *Cured.* If the patient was free of symptoms and presented no objective evidence of psychoneurosis.

3. *Improved.* If the symptoms were less in intensity or frequency and the work record was improved, the patient was placed in this group.

4. *Unchanged.* If there was no subjective or objective change in the patient's psychiatric condition, he was classified as unchanged.

5. *Worse.* If there was progression of the neurosis as evidenced by increase in intensity or frequency of symptoms, decreased work capacity, or necessity for institutional care.

6. *Dead.* The cause of death is given and when possible is correlated with the original diagnosis and complaints.

Table 6 shows the end results in the group of patients examined, the patients in state institutions and the deaths.

TABLE 6.—RESULTS.

Group.	Incorrect diagnosis.	Cured.	Improved.	Unchanged.	Worse.	State Hosp.	Death.
Much psychiatric care	1 (?) 2.9%	0 0%	10 28.6%	13 37.1%	6 17.1%	4 11.4%	1* 2.9%
Some psychiatric care	2 2.8%	1 1.4%	22 31%	26 36.6%	13 18.4%	4 5.6%	3 4.2%
No psychiatric care	13 13.8%	7 7.4%	13 13.8%	41 43.6%	8 8.5%	1 1.2%	11 11.7%
					27	9	
Total	16 8%	8 4%	45 22.5%	80 40%	36 18%		15 7.5%

* One patient (M. R. 9805) was classified as improved at the time of follow-up examination. Several months later, however, before our study was completed, he died, and is therefore listed under the deaths.

Original Diagnosis of Psychoneurosis Incorrect. In the group receiving much psychiatric care Case 6544 is noteworthy. In addition to many visits to the medical clinic, she was seen in 14 other clinics and made 5 psychiatric visits during the years 1933 to 1939. The original psychiatric impression was psychoneurosis with hysterical features superimposed on a psychopathic personality. The medical diagnosis was psychoneurosis, migraine and epilepsy. At the time of the follow-up examination in February, 1939, the patient's chief complaint was convulsions. It was found that she had a positive blood serology and a positive spinal fluid with a paretic type of gold curve. Although the patient did exhibit certain hysterical personality traits there has been such a marked improvement following malarial and other antiluetic therapy that it was felt justifiable to place the patient in this group.

The 2 patients receiving some psychiatric care, Cases 7800 and 3041, were felt on reëxamination to show no evidence of psychoneurosis. Both the medical and psychiatric examiners agreed that the symptoms were on a physical basis without any appreciable emotional component. The one patient has Paget's disease of the bone, the other has hypertensive and arteriosclerotic heart disease.

Four of the 13 patients in the non-psychiatrically treated group were found to be perfectly well. Recovery in these patients followed the proper treatment of organic disease unrecognized during the first year of dispensary attendance. (1, Ileocolostomy and resection for terminal ileitis; 2, cholecystectomy with removal of a chronically inflamed gall bladder with stones; 3, high vitamin, high calcium diet in a malnourished patient with poor dietary habits; 4, adequate iron therapy in a patient with idiopathic hypochromic anemia.) The other 9 patients in the non-psychiatrically treated group were thought to be suffering entirely from organic disease without significant personality difficulties. These disorders were: 1, coronary artery disease, 2 cases; 2, cardiovascular syphilis, 1; 3, rheumatic heart disease, 1; 4, pernicious anemia with subacute combined sclerosis of the cord, 1; 5, arthritis, 2; 6, postencephalitic Parkinsonism, 1; 7, lumbosacral strain, 1.

The errors in this group could have been avoided if the physician had been aware that positive evidence of neurotic personality traits and neurotic behavior is essential for a diagnosis of psychoneurosis. It should never be made solely on the basis of the exclusion of organic disease, for it is this common practice which frequently results in a postponement of the correct diagnosis until such a time as therapy may be of no avail. Far more prudent is a modest confession of ignorance of the diagnosis rather than a diagnosis of psychoneurosis in the patient with unexplained complaints without evidence of neurotic personality traits.

Cured. Six of the 8 patients cured were gainfully employed. These patients had undergone favorable environmental changes

which undoubtedly caused a resolution of the neurotic manifestations. In 4 of these the changes were improvement in the patient's economic status; in the fifth, separation from an incompatible wife. The sixth patient with almost complete loss of hearing had obtained a satisfactory hearing aid. In 2 patients the factors involved in the resolution of the neurotic process could not be ascertained.

Improved. In 33 patients, irrespective of whether they had received psychiatric treatment or not, improvement appeared to be related to changed circumstances, *e. g.*, it followed some favorable change in the patient's environment, social status or personal relationships. The commonest of these changes are given below:

1. Changes in occupation, *e. g.*, more pay, better working hours, better working conditions, more congenial employer or working companions, more desirable geographical location.

2. Changes in social status, *e. g.*, marriage, re-marriage, or separation or divorce from incompatible partners.

3. Death of burdensome or antagonistic relatives or emancipation from them through departure from the home, *e. g.*, invalid mother, mother-in-law and so on.

4. The adoption of a child in sterile marriage.

5. Changes in sexual drive due to advancing age.

In a smaller number (8 patients) improvement was due to spontaneous recovery from minor organic ills (*e. g.*, subsidence of menopausal symptoms) or to improvement of these ills due to medical treatment and/or better insight into the illness through psychotherapy.

One patient's improvement was attributed to the adoption of Christian Science.

In 4 patients showing some improvement there still existed a vicious circle of somatic and neurotic factors.

Unchanged. Eighty of the patients interviewed showed no evidence of change in their psychiatric status. This represents the largest group and confirms the current belief that when firmly established the fundamental attitude and behavior pattern of psychoneurotic patients is unaltered by external influences.

Worse. Thirty-six of the patients interviewed showed progression of their neuroses. Of these, 9 required care in psychiatric institutions. Of the remaining 27, 21 showed no evidence of co-existing organic disease and the patient's ill-health was attributed solely to the progression and fixation of the neurosis.

In 6 patients, increase in the symptoms seemed due to both a progression of the organic disease and the neurosis. One of these patients, Case 48603, is worthy of mention, for during the 5-year period polycystic disease of the kidneys and liver was recognized. The follow-up examination revealed abundant evidence of deep-rooted hypochondriacal trends with beginning depressive and paranoid features in addition to the organic disease.

None of the 9 institutionalized patients were interviewed. Eight had had psychiatric interviews at The New York Hospital during the first year of their admission to the Out-Patient Department. Four of the 9 patients were diagnosed in the State Institution as suffering from dementia præcox, 4 from psychoneurotic disorders (1 complicated by chronic alcoholism), and 1 from a depressive psychosis.

Deaths. The deaths are listed in Table 7.

TABLE 7.—DEATHS.

Hist. No. of patient.	Age.	Original Out-Patient Dept. diagnosis (1933-34).	Cause of death and date.	Autopsy.
45845	55	Hypochondriasis and anxiety state; syphilis (treated)	Suicide, 1935	Medical examiner
286*	65	Anxiety state (?petit mal attacks)	Cancer of breast, skeletal metastases, 1938	Not done
21238	43	Psychoneurosis, polycythemia vera	Leukemia following polycythemia, 1936	Montefiore Hospital
9719	60	Psychoneurosis with anxiety features; hypertension	Carcinoma of lung, 1937	Not done
18796	31	Nervous indigestion	Influenzal pneumonia with multiple lung abscesses, 1937	At New York Hospital
3141	24	Psychic trauma	Accidental (auto accident)	Medical examiner (up-state)
19144	33	Neurasthenia with chronic invalidism	Leukemia, 1937	Not done
10342	45	Psychoneurosis with depressive features	Lobar pneumonia complicated by chronic alcoholism, 1936	Not done
14952	27	Nervous fatigue	Pneumonia, 1938	Not done
22646	52	Psychoneurosis and hypertensive cardiovascular disease	Coronary thrombosis	Not done
29633	23	Neurasthenia	Postoperative death; duodenal ulcer, cholelithiasis, hemorrhage, 1934	At Polyclinic Hospital
16948	46	Anxiety neurosis	Suicide when in Bronx Hospital for terminal cancer of lung, 1937	Medical examiner
26406	35	Psychoneurosis; hypertension	Cerebral hemorrhage	Not done
3738	64	Anxiety state caused by financial stress	Bronchopneumonia complicating arteriosclerotic heart disease, 1934	Not done
9805	32	Allergic asthma; bronchiectasis, psychoneurosis	Bronchopneumonia; ? pulmonary fibrosis, 1938	Not done

* Psychiatric consultant did not confirm the original diagnosis of anxiety state in this patient, but thought the condition was entirely due to epilepsy and its equivalents.

Analysis of the deaths reveals that: 1. In no instance can it be said with certainty that the patient died of an illness present but unrecognized at the time of the original diagnosis. In Case 29633 it is probable that the duodenal ulcer for which the operation was performed was present but unrecognized in 1933. In Case 286, however, it is highly improbable that the patient's chief complaint of headache was due to the bony metastases from the carcinoma of the breast. The primary tumor was not recognized until 1937, and the bony metastases were demonstrated by Roentgen ray shortly thereafter. This case is further complicated by hypertensive cardiovascular disease which in itself might account for the headaches.

2. Four patients died of causes related to the organic disease diagnosed on the original visit (Cases 21238, 22646, 26406, 9805).

3. Eight patients died of unpredictable causes, the commonest of which was pneumonia.

4. In 2 cases death occurred by suicide (Cases 45845 and 16948). In 1 of these the precipitating factor was incurable cancer of the lung.

Organic Disease Discovered at Time of Follow-up Examinations. The organic disease in this group is believed to have been present but unrecognized at the time of the original examination. It is not the purpose of this paper to emphasize the diagnostic frailties during 1932 and 1933. However, cases with unrecognized organic disease are summarized in one table for purposes of simplification.

Cured Group—4 Cases.

1. Terminal ileitis
2. Chronic cholecystitis and cholelithiasis
3. Idiopathic hypochromic anemia
4. Malnutrition with vitamin deficiency

Improved Group—4 Cases.

1. Gastritis
2. Rheumatic heart disease with mitral stenosis, Class I
3. Hypertensive cardiovascular disease
4. Arteriosclerotic heart disease

Unchanged—6 Cases.

1. Hypertensive cardiovascular disease
2. Diaphragmatic hernia
3. Latent syphilis
4. Hypertensive cardiovascular disease
5. Migraine (2 cases)

Worse—5 Cases.

1. Polycystic kidneys and cystic liver
2. C.N.S. syphilis
3. Cardiovascular syphilis (2 cases)
4. Cholecystitis and cholelithiasis

The occurrence of unrecognized syphilis is no doubt due to the omission of the routine Wassermann test in the Medical Clinic prior to 1935. The organic disease discovered in 2 patients, the one with rheumatic heart disease, Class I, and the other with congenital diaphragmatic hernia, is thought to be an incidental finding unrelated to the patient's symptoms and complaints.

Follow-up Cases Not Interviewed. Data in this group were obtained from 69 patients, either through correspondence or home visits by the social service worker. They are not amenable to the careful analysis of the interviewed group and are therefore tabulated without detailed comment.

TABLE 8.—FOLLOW-UP CASES NOT INTERVIEWED.

	Incorrect diagnosis.	Cured.	Improved.	Unchanged.	Worse.
Much psychiatric care	0	0	2	1	0
Some psychiatric care	1	4	9	6	0
No psychiatric care	0	16	14	10	6
	—	—	—	—	—
Total	1 (1.4%)	20 (29%)	25 (36.2%)	17 (24.6%)	6 (8.8%)

The much higher percentage of patients cured and improved in the correspondence group as contrasted with the interviewed group (65.2% contrasted with 27%) may be due to a variety of causes, none of which can be unequivocally proven. The commonest reasons given for refusal to attend the follow-up examinations were: 1, the patient felt perfectly well and saw no necessity for the examination; 2, difficulties were encountered in securing time off from work in order to attend the interview; 3, dissatisfaction with previ-

ous care and failure to be benefited thereby. From the first two of these reasons one would predict a larger percentage of cured or improved patients in the correspondence group. This is further substantiated by the fact that in the interviewed group it was noted that the patients with the most severe and deep-seated neuroses frequently responded earlier and more enthusiastically to the request for interview than the patients who were less mentally disturbed.

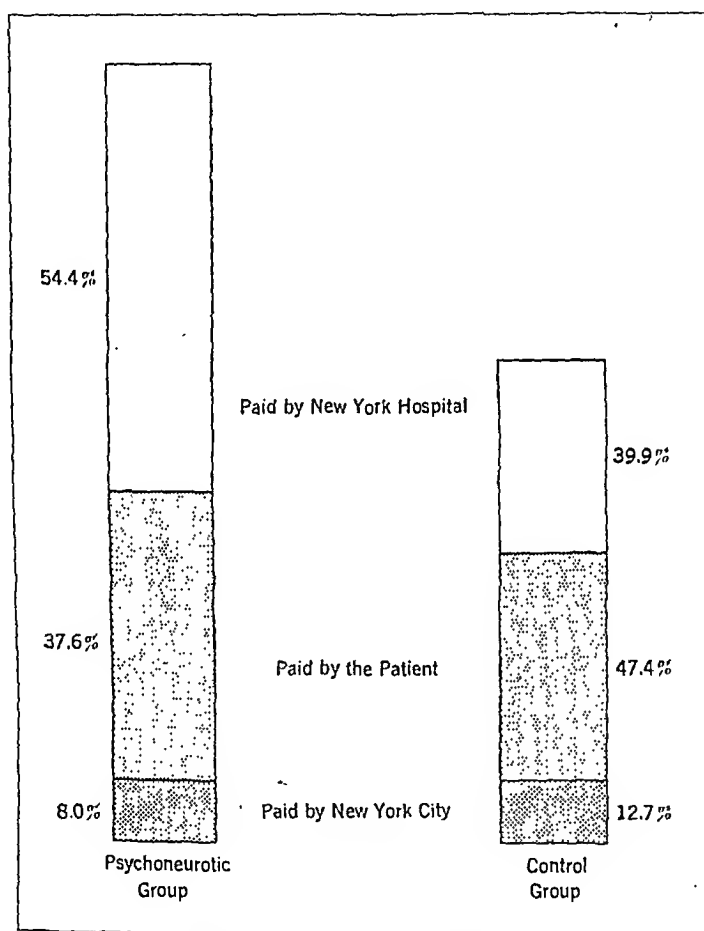


CHART 3.—Cost for patient care.

Cost of Medical Care. The cost of medical care during the study period for the 269 psychoneurotic patients was \$16,345, the average cost per patient being \$60.76. Of this amount 54.4% was paid by The New York Hospital; 37.6% by the patients; and 8% by the Department of Welfare of the City of New York. In the control group the average cost per patient was \$37.18, or 61.2% of the cost of the care for the psychoneurotic patient. The distribution of the cost in the control group was as follows: 39.9% paid by The New York Hospital; 47.4% by the patient, and 12.7% by the Department of Welfare of the City of New York. These data show that

the cost of medical care to patient and to hospital is higher for psychoneurotic patients than for those with organic disease. This is illustrated in Chart 3.

In an effort to learn if this increased cost is justified, the cost was correlated with the clinical results at the end of the 5-year period. This is shown in Table 9.

TABLE 9.—COST OF MEDICAL CARE.

Results.	No. of patients.	Average cost per patient.
Original diagnosis incorrect	17	\$158.18
Cured	28	30.71
Improved	71	48.14
Same	96	56.91
Worse	43	49.34
Deaths	15	95.86

The average cost was greatest for patients in whom the original diagnosis was incorrect. This is explained by the frequent hospitalization for investigation of patients in whom the diagnosis was obscure. Of this group 5 spent 112 days on the Pavilion at an average cost of \$326 per patient. The cost was least for those patients that were cured, and increased as the result became less favorable. It is apparent therefore that in the psychoneurotic patient the cost of medical care is not proportional to the clinical result.

Clinics Attended. The cost of medical care is directly related to the number of clinics attended. This is shown in Table 10.

TABLE 10.—RELATION OF COST TO NUMBER OF CLINICS ATTENDED.

No. of clinics.	No. of patients.	Average cost per patient.
1	48	\$12.43
2	64	39.79
3	48	30.48
4	39	49.38
5	20	38.45
6	20	152.50
7	8	205.00
8	8	149.00
9	4	215.00
10	3	206.67
11	2	309.98
12	3	333.66
15	1	217.00
20	1	459.00

An effort was then made to correlate the number of clinics attended with the end-results. This is shown in Chart 4.

These data show that a higher proportion of psychoneurotic patients were cured or improved in the group attending 5 or less clinics than in the group attending 6 to 20 clinics. It also shows that a higher proportion are the same or worse in those attending 6 or more clinics. Since attendance in more clinics does not contribute to the therapeutic result and does increase the cost of

medical care, it appears that it would be better to care for patients in as few clinics as possible.

Outside Cost. An effort was made to determine the medical costs other than those contracted at The New York Hospital. The patients' unwillingness or inability to give an accurate statement of this, however, made only a rough estimate possible. It was found that 77 (28.5%) were treated only at The New York Hospital, whereas 109 (40.4%) had visited other clinics, had consulted private doctors or had called ambulance or Relief doctors; 84 (31.1%) gave no information.

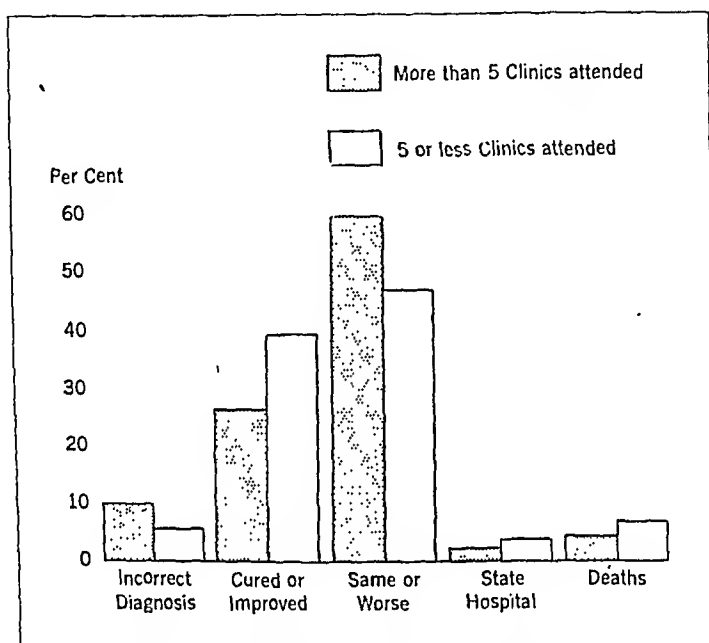


CHART 4.—Correlation of clinics attended and end-results.

Summary of Medical Costs. Study of the medical costs of psychoneurotic patients raises several interesting problems, not the least of which involves the justification for the greatest expenditure on a group that shows little or no improvement over a period of 5 years. Some of the poor results are no doubt attributable to the inherent nature of the disease. Efforts to improve the results by referring the patients to various special clinics were largely futile and partly account for the increased cost of medical care. This suggests that the static therapeutic results and the high cost may be influenced by altering the method of management of these cases in the clinic system at The New York Hospital.

Discussion. From this study were developed certain suggestions for improvement of the care of psychoneurotic patients, some of which are already in effect. In the past 5 years more time and energy have been devoted to teaching medical students and resident

and clinic physicians how better to deal with psychoneurotic patients. The importance of this becomes obvious when it is recognized that most of the mistakes made are the inevitable sequelæ of the physician's ignorance of, or attitude toward, psychoneurotic disorders. The psychiatric consultants in the medical clinic have been increased from 2 to 5 and a resident psychiatrist who devotes most of his time to consultation problems in the general hospital has been provided. Fourth-year medical students during their clerkship in the Out-Patient Department are increasingly aware of the emotional and environmental factors in illness and are less inclined to label every patient with personality difficulties as a "crock." In an 8-week clerkship the students often obtain excellent therapeutic results in patients who are impressed by the "doctor's" interest and understanding of their case. In a few interviews the internist or the medical student can often make life more tolerable for these patients though a permanent cure is rarely achieved. It may be necessary over a period of years for the doctor to repeatedly explain to the patient the nature of his illness and the mechanism of his symptoms. It cannot be overemphasized, however, that any method of therapy that permits these patients even a temporary respite from constant medical attention is therapeutically sound. This view is substantiated by the absence of dramatic therapeutic results in patients under prolonged treatment in the psychiatric clinic.

In the management of psychoneurotic patients in a general medical clinic, a few simple principles are advocated:

1. The old concept that a disease is either functional or organic should be abandoned; it should be recognized that both functional and organic diseases occur in the same patient with great frequency.
2. The diagnosis of psychoneurosis should never be made solely as an exclusion diagnosis, *e. g.*, based on a failure to find evidence of organic disease. It necessitates the presence of definite neurotic personality traits and behavior which may manifest itself as anxiety, hysteria, hypochondriasis, phobias, ties or obsessive states.
3. The type and extent of organic disease should be established early.
4. The physician should consult with a psychiatrist and a social worker early in order to determine whether extensive psychotherapy is advisable and whether environmental or social handicaps can be lessened or removed. This is considered important since the poor results in the psychiatrically treated group may be due in part to an unfortunate selection of cases. Some patients with deep-seated psychoneurotic disorders receive little benefit from therapy in the psychiatric out-patient department and for this reason may be referred back to the internist for superficial psychotherapy. A great service is rendered these patients if the internist will treat them with supportive measures and see them as often as is necessary to prevent medical shopping.

5. When it is necessary for both the psychiatrist and the internist to see the patient over a long period of time it is of importance that they consult occasionally, particularly before any major therapeutic changes are undertaken, *e. g.*, elective operations or treatment in new clinics.

6. The patient should have but one physician. When consultations with specialists are necessary they should be held in the presence of the referring doctor. This minimizes the confusion so often arising from conflicting opinions and advice.

Many patients are cared for indefinitely in the clinic when there is little or nothing to be gained by continued attendance and repeated examinations. Much time, money and energy are wasted through this practice. It was not an uncommon experience to find in 15 minutes' conversation with the patient that in years of clinic attendance no one had given the patient a simple explanation of his illness or told him that he could do as much for himself at home as the doctor could in seeing him repeatedly in the clinic. Some patients learn this through a process of trial and error.

An effective system should be developed to discourage medical shopping in the various institutions and clinics throughout the city. This practice with its duplication of examinations is an economic waste, increases the cost of medical care and is detrimental to the patient's welfare. The problem is one which cannot be solved by any one institution; the solution rests with the local (city) medical society. In New York City these patients represent but one group who would benefit if the present system of medical care were re-organized in such a way that there would be centralization of local responsibility and simplification of the coöperative service rendered by the Department of Welfare, private hospitals and the charity and industrial organizations.

Summary. In a general medical clinic 269 consecutive patients with the diagnosis of psychoneurosis were reinvestigated after the elapse of 5 years. Sixty-seven (25%) patients had coëxisting major organic disease at the time of the original interview; 129 (48%) received psychiatric treatment varying from 1 to 110 psychiatric visits, the average being 6. Five years later, 80 (40%) patients showed no change in their psychiatric status, 45 (22.5%) were improved, 36 (18%) were worse, 8 (4%) were cured, 15 (7.5%) had died and 16 (8%) had been incorrectly diagnosed as psychoneurotic. There was no noteworthy difference between the psychiatrically and non-psychiatrically treated groups but this was thought to be due in part to unwise selection of cases for psychiatric treatment. Better therapeutic results were obtained in those patients who attended few clinics than in those who attended many clinics. The cost of medical care increased in proportion to the number of clinics attended.

Suggestions have been made for the improvement of the care of

psychoneurotic patients. Among these is an educational program which emphasizes to medical students, resident and out-patient department physicians, the importance of the patient's personality in relation to his illness. The referral of psychoneurotic patients from clinic to clinic, largely due to the unwillingness of the physician to deal with unpleasant personalities, is a pernicious habit which should be discouraged. It adds to the cost of medical care and jeopardizes the patient's chance of cure.

It is believed that the internist with adequate training, the proper attitude and a suitable clinic organization can, in a few concentrated interviews, make life more tolerable for many psychoneurotic patients although he can cure relatively few. This can be accomplished with a maximum economy of time and money for the patient and effort for the physician if the patient has but one doctor.

Psychiatric interviews were carried out by Dr. Phyllis Greenacre and Dr. Emeline Hayward of the Department of Psychiatry of the Payne Whitney Clinic. Social Service contacts and investigation were carried out by Miss Alice Fahmy of the Social Service Department of The New York Hospital.

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THE TREATMENT OF CERTAIN MUSCULAR ATROPHIES WITH VITAMIN E, WITH A NOTE ON DIAGNOSIS AND THE ELECTROMYOGRAMS.*

BY HENRY R. VIETS, M.D.,
NEUROLOGIST.

E. H. TROWBRIDGE, JR., M.D.,
RESIDENT PHYSICIAN IN NEUROLOGY,

AND

T. E. GUNDERSEN, M.D.,
RESIDENT PHYSICIAN IN NEUROLOGY,
BOSTON, MASS.

(From the Department of Neurology, Harvard Medical School, and the Massachusetts General Hospital.)

A PRELIMINARY clinical report by Wechsler^{8a} in March, 1940, on 2 patients with amyotrophic lateral sclerosis, showing favorable results after treatment with vitamin E, has led to a widespread clinical trial of this vitamin in certain forms of muscular atrophy. Many reports^{1-4,7} are now available, not only on the treatment of

* Read in part before the Boston Society of Psychiatry and Neurology, March 20, 1941.

amyotrophic lateral sclerosis with vitamin E, but its use in other intrinsic, degenerative diseases of the spinal cord, as well as in cases of dystrophy and peripheral neuritis. Vitamin E has been used in its synthetic state, alpha-tocopherol acetate, by mouth and by intramuscular injection; as wheat-germ oil; and in the form of foods rich in vitamin E. Wechsler,^{8b} in his second report, used all methods. Slowly there is being evolved a considered opinion, both in regard to vitamin E itself and its effect on various diseases.

At the Massachusetts General Hospital we selected a few patients for treatment, using those whose chief symptoms were atrophy and fibrillation of muscles. Vitamin E was used in the form of alpha-tocopherol acetate,* given either by mouth or subcutaneously. Eleven cases diagnosed as amyotrophic lateral sclerosis, 6 cases of progressive muscular atrophy and 4 of peroneal muscular atrophy of the Charcot-Marie-Tooth type were treated over a period of 10 months between April, 1940, and February, 1941, inclusive. Some patients were observed 4 months after treatment was discontinued.

All the 21 cases are summarized in Table 1. Seven case histories, however, are given as illustrative of the group as a whole.

Case Reports. CASE 1.—*Amyotrophic Lateral Sclerosis*. E. S. (223490), a carpenter, aged 42, noticed some "stiffness" in his left hand 12 months prior to entry. Weakness developed in his hand within 3 months followed by stiffness and weakness of his legs about the same time. His family and past history were non-contributory to his present illness.

On examination, atrophy of the small muscles of the hands and of the shoulder muscles was observed, the atrophy being more pronounced on the left than the right. Fibrillary twitchings were observed in all the atrophic muscles. His legs were spastic, without atrophy. The reflexes were brisk and equal in the arms; in his legs, the reflexes were greater on the left than the right and an ankle clonus and Babinski sign were elicited on the left side. There was hypalgesia of the ulnar areas of both hands and forearms. A spinal cord tumor was suspected, because of the sensory changes and a reported lipiodol "block" at the level of the fifth cervical spinal cord segment; a laminectomy at this level failed to disclose any lesion.

Following operation, vitamin E was given for more than 9 months by mouth. The dosage, begun at 20 mg. a day, was increased at intervals of 8 weeks to 250 mg. a day. He took the final dosage of 250 mg. a day for 14 weeks. His condition appeared to improve slightly at the start of the treatment, but shortly no further change was noted. The disease at the end of 9 months was stationary.

CASE 6.—*Amyotrophic Lateral Sclerosis*. L. B. (249423), a machinist, aged 43, entered the hospital in May, 1940, because of atrophy and weakness of the right hand of 3 years' duration. There was atrophy of the thenar muscles in the right hand and some weakness on the left. Fibrillations were present in both shoulders. The arm reflexes were hyperactive, Hoffmann sign was present on both sides and, although the legs were not weak, there was a bilateral Babinski sign. The spinal fluid was normal.

Vitamin E, by mouth, was given in doses of 50 to 200 mg. daily over a period of 6 months. There was no change in the clinical findings at the end of the treatment period.

* Kindly furnished by Hoffmann-LaRoche, Inc.

*Electromyograms.** In May, 1940, before treatment with vitamin E was started, 30 to 40 fibrillations per minute were recorded from the right deltoid muscle by surface electrodes. In July, 1940, the count over the same muscle was 10 to 12 and in October, 1940, after being under treatment for 5 months, no fibrillations were recorded. In December, 1940, 3 months later, the count was 50. The vitamin E was stopped at this point. In January, 1941, 14 fibrillations were counted and in April, 20 per minute were seen in the electromyogram. All counts were taken under similar circumstances of environment and from approximately the same points on the muscle.

TABLE 1.—CASES TREATED WITH VITAMIN E FROM APRIL, 1940, TO JUNE, 1941.

No.	Initials.	Case No.	Age.	Sex.	Months of disease.	Weeks of treatment.	Result.
<i>Amyotrophic Lateral Sclerosis.</i>							
1	E. S.*	223490	42	M	12	38	Unchanged
2	W. M.	212848	39	M	11	8	Died
3	F. B.	172564	48	F	12	8	Worse
4	G. K.	239472	51	F	12	18	Died
5	G. D.	250632	67	M	4	10	Died
6	L. B.*	249423	43	M	36	28	Worse
7	D. T.	13562	61	F	60	12	Unchanged
8	L. W.	250543	45	M	24	18	Unchanged
9	K. G.*	103084	61	F	12	29	Worse
10	J. M.	254899	70	M	3	4	Died
11	F. C.*	242214	43	M	12	4	Died
<i>Progressive Muscular Atrophy.</i>							
12	S. K.	249990	53	M	18	23	Worse
13	L. G.	250639	30	M	18	9	Unchanged
14	J. P.*	98482	53	M	6	34	Worse
15	M. M.	14510	43	F	36	38	Worse
16	W. P.*	270257	66	M	36	15	Died
17	F. A.	256973	34	M	7	9	Unchanged
<i>Peroneal Muscular Atrophy.</i>							
18	L. P.	237194	30	M	(years)	36	Unchanged
19	A. E.*	239571	43	F	3	36	Worse
20	D. M.	240800	35	M	(years)	8	Unchanged
21	T. D.	255189	19	M	36	13	Unchanged

* Case histories abstracted in the paper.

CASE 9.—*Amyotrophic Lateral Sclerosis.* K. G. (103084), a Finnish housewife, aged 61, entered the hospital August 16, 1939, with a complaint of weakness in both arms for a period of 1 year. Atrophy and fibrillations were noted in the deltoid and triceps muscles, bilaterally and also in the muscles of the tongue. The triceps reflexes were moderately active, but the biceps and those in the legs were very brisk. Both the Hoffmann and the Babinski sign were present. Treatment with vitamin E was begun in May, 1940, and continued for over 7 months; the dosage, beginning at 50 mg. a day, was increased in the last weeks of treatment to 250 mg. The patient grew slowly worse.

CASE 11.—*Amyotrophic Lateral Sclerosis.* F. C. (242214), a single mill-worker, aged 43, entered the hospital March 25, 1940, with a complaint of weakness of his right arm and right leg of 1 year's duration. The first symp-

* All the electromyograms were taken by Robert S. Schwab, M.D., Director of the Encephalographic Laboratory of the Massachusetts General Hospital. I am indebted to him for the reports and the figure used to illustrate Case 16.

tom was an unsteady gait due to weakness of the right leg. The arm became weak 9 weeks before entry. The patient had suffered from epilepsy since the age of 14. The examination on entrance showed spasticity of both legs, the right being more affected than the left. Deep tendon reflexes of the legs were increased above the normal; patellar and ankle clonus were present, with a Babinski sign on the left and a less marked Babinski sign on the right. The Romberg sign was not elicited. Both arms were weak, the right more than the left. Atrophy and fibrillation were present in both arms, but less evident in both legs.

On the first admission, wheat-germ oil was given in the concentrated form, 1 teaspoonful, 3 times daily.

The patient was readmitted December 8, somewhat worse, with increasing difficulty in gait, additional weakness of his arm, marked fibrillations and atrophy, and dysarthria. There was weakness of the tongue and fibrillations. Intensive vitamin E treatment was begun, the patient taking up to 450 mg. a day by mouth, with 50 mg. by intramuscular injection, 3 times a week. He was discharged December 23, and died at home, of respiratory paralysis, January 7, 1941.

Electromyograms. On December 9, 1940, the fibrillations varied from 12 to 20 per minute. On December 23, they were 30 to 40 per minute.

CASE 14. *Progressive Muscular Atrophy.* J. P. (98482), a male, aged 53, entered the hospital November 20, 1939, complaining of weakness of his right leg of 6 months' duration. The examination showed, besides an atrophic, flaccid right leg below the knee, weakness of both legs and arms with fibrillations of the muscles of both thighs and shoulders. There was foot-drop on the right side. Syphilis had been contracted 22 years before entrance to the hospital, but an examination of the spinal fluid was negative for any signs of the disease. Wheat-germ oil was given in March, 1940, and vitamin E was taken after September of the same year. The disease progressed without remission and in March, 1941, when treatment was discontinued, the patient was bedridden.

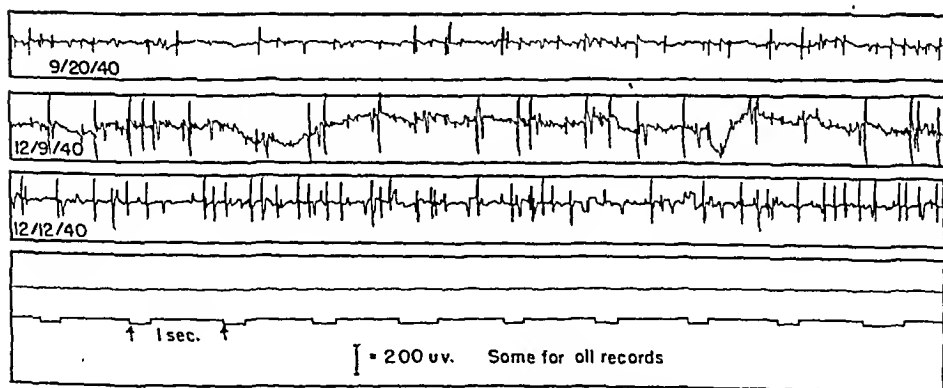


FIG. 1.—Electromyograms of Case 16, progressive muscular atrophy. Taken with surface electrodes from the right deltoid muscle. The first record was taken before vitamin E was used; the second and third during treatment. There was a progressive increase in the number of fibrillations: 240, 350, 390 per minute. The patient died 1 month after the last record was taken. (Schwab and Skogland, courtesy of Journal-Lancet.)

CASE 16.—*Progressive Muscular Atrophy.* W. P. (270257), a lawyer, aged 66, entered the hospital September 15, 1940, complaining of weakness of his legs and back of 2 months' duration. Nearly a year before entrance the patient showed signs of posterior column disease, with ataxia, paresthesias and lightning pains. A diagnosis of tabes was considered in spite of a

normal pupillary response and no changes in the blood or spinal fluid. Examination on entrance indicated a new set of signs. There was marked fibrillation of all muscles in the shoulder girdle, the muscles of his legs and slight fibrillation of the left side of his tongue. The sensory symptoms noted the year before were in abeyance. Vitamin E, 150 mg. daily, was given at the start, soon increased to 200 mg. and later to 300 mg. per day, partly by intramuscular injection. The patient grew rapidly worse and died January 12, 1941.

Electromyograms. Before treatment the right deltoid showed 240 fibrillations per minute. On December 9, 1940, the count was 350 and on December 12, 390 per minute.

CASE 19.—Peroneal Muscular Atrophy. A. E. (239571), a Finnish housewife, aged 43, entered the hospital April 18, 1940, because of progressive difficulty in walking of 3 months' duration. The weakness began insidiously, with dragging of the right leg and inability to climb stairs. Examination disclosed a generalized weakness of all the leg musculature, with the greatest loss in the tibial and peroneal groups. There was foot-drop, as well as inability to walk on the toes. The gait was of the slapping, steppage type. No fibrillations were observed. The knee jerks and ankle jerks were present, but slight. No loss of sensation was recorded.

Treatment with vitamin E was given for 3 months, beginning with 20 mg. per day and ending with 250 mg. per day, for the last 12 weeks. During this period the disease progressed steadily. By January, 1941, walking was almost impossible and weakness in the arms was evident. Her condition in March, 1941, was even less satisfactory.

The Diagnosis of Amyotrophic Lateral Sclerosis and Allied Conditions. The diagnosis of the intrinsic "system" diseases of the spinal cord is no longer a simple procedure, for the exact conditions described by Duchenne, Charcot and others have been superseded by syndromes, containing the usual motor elements, but in atypical and even bizarre forms. Charcot describes amyotrophic lateral sclerosis, for instance, as a disease of the motor system, beginning with an atrophic, flaccid, symmetric paralysis of the small muscles of the hands. The disease progressed rapidly up the arms to the shoulders with later, but less extensive, involvement of the legs, the chest muscles, and the diaphragm. The order of progress seldom varied; the symmetry almost never. The disease was entirely motor, all sensory elements being absent, including pain, paresthesias or ataxia. The lateral tracts were also diseased, conspicuously in the cervical region, but degenerated in their entire length. The legs, therefore, were spastic with an increase in the deep reflexes and ankle clonus. Long after Charcot's time the Babinski sign was added as a clinical finding. In the later stages of the disease the legs often presented the unusual condition of a combination of atrophic and spastic paralysis, the former usually overcoming the latter. The sphincters were never primarily affected. The picturesque name, combining a clinical sign with a pathologic finding, was the one originally used by Charcot (1869).

The original descriptions of progressive muscular atrophy are even older than those of amyotrophic lateral sclerosis. Duchenne (1849) and Aran (1850) described the spinal type and Duchenne

(1861), alone, the bulbar form. The diseases are much alike except for the absence of lateral sclerosis and its spastic manifestations in the legs in progressive muscular atrophy. When progressive muscular atrophy began as an affection of the tongue and throat, moreover, causing dysarthria with its characteristic "hot-potato" speech, the disease was called bulbar paralysis. Frequently bulbar paralysis, as described above, was associated with progressive muscular atrophy, or, more rarely, with amyotrophic lateral sclerosis.

If the clinical descriptions of these three diseases were thought to be rigid and exact, the reports of the pathologic lesion were even more so. "Systems" were involved exclusively and the diseases were classed as "system diseases" above all others. The "systems" were the anterior horn cells column of the spinal cord, extending up into the medulla and bulb as the nuclei of the lower cranial motor nerves, and the lateral or "pyramidal" tract. The latter was only involved in one of the three diseases, namely, amyotrophic lateral sclerosis. No other parts of the nervous system were affected.

To these rigid classifications we no longer adhere. Diseases are becoming syndromes, not only in their multiple causes, but also in their symptomatic variability. In cases of progressive muscular atrophy or amyotrophic lateral sclerosis, symmetry is no longer considered essential to the diagnosis. The disease may, moreover, begin in the shoulder, trunk or even in the legs. One arm or one leg may be affected far in advance of its fellow, or one arm and one leg may become involved simultaneously. Steady progress in the disease, once considered as a nearly constant feature, is, in addition, now regarded as usually characteristic, but not invariably so. Many cases have been reported with long remissions: others with short and even repeated remissions. Remissions, however, do not consist of periods of improvement, but in a temporary secession of clinical advancement. Continued relapse is still the rule; intermittent relapse, the exception.

When sensory symptoms are reported, however, the diagnosis must be seriously questioned. If we wish to uphold the ordinary categories of descriptions of clinical entities, we must not make too broad exceptions. Sensory symptoms of any kind in bulbar paralysis, progressive muscular atrophy or amyotrophic lateral sclerosis cannot be allowed, except on the basis of some other coincident disease. It is, in part, due to the inclusion of patients with sensory symptoms that has led in recent years to false reports of recovery following various types of treatment. Certain forms of neuritis, particularly neuronitis, involvement of the anterior and posterior roots of the spinal cord, and the upper portions of the great plexuses, almost always with some sensory symptoms, although closely resembling in their clinical manifestations the system diseases, have been called, erroneously, progressive muscular atrophy or amyotrophic lateral sclerosis. A most searching investigation is needed

to separate these groups, one so likely to respond to vitamin therapy and the other, the intrinsic cord disease, so invariably unaffected by any known treatment. This is one of the features, therefore, that has tended to confuse our opinion, if based on the current literature, regarding the efficiency of vitamin therapy. A more careful and strict diagnosis would have led, in some cases, to a less sanguine report on the value of vitamin E in the treatment of the system diseases.

Another point, moreover, has often arisen regarding diagnosis. This is based on our dependence upon fibrillation as an unequivocal sign of anterior horn cell, or similarly, cranial nerve motor nuclei, degeneration. Fibrillation is uncontrolled twitching of the muscular units, or small groups of muscle fasciculi, of the voluntary muscles undergoing atrophic, flaccid paralysis. It is almost exclusively associated with slow degeneration or dysfunction of the motor cells of the lower motor neuron. Not characteristic of poliomyelitis, an acute process, but invariably a part of the three system diseases under consideration, fibrillation may also be a sign of the more peripheral diseases, the various forms of neuritis. In the system diseases, however, it is often persistent, widespread and has a rippling, wave-like quality, not seen in neuritis. It often precedes any marked paralysis, but atrophy is usually obvious when fibrillation is present. Rare twitches are the rule in neuritis; nearly continuous activation in bulbar palsy, progressive muscular atrophy and amyotrophic lateral sclerosis. The fibrillations may be easily recorded on an electromyogram, but there is nothing characteristic about the changes in electric potential and electromyograms are not diagnostic of individual diseases. If they can be recorded electrically, moreover, they can usually be seen clinically. The myographic method, however, is a convenient way of making a permanent record and serves also as a means of counting the number of fibrillations in a given unit of muscle.

If we extend our diagnosis, therefore, beyond the strict limits set down by Charcot and his contemporaries, as is customary at the present time, less dependence on an exact diagnosis must be expected. This conforms to the trends in neurology in fields other than the system diseases and leads to a broader outlook on what we used to call "clinical entities." An older neurologist once said: "I no longer make diagnoses; I think in terms of syndromes." All is well if only the senior neurologist takes this point of view; the junior falls into many traps if he does not stick to diseases. It is best to describe the simple diseases as exact diagnoses and then point out any unusual feature, without extending the diagnosis far afield into the "atypical" territory. In reviewing the recent literature on the treatment of these system diseases with vitamin E, one is conscious that not a few diagnoses fall into the "atypical" field and thus are doubly difficult to use as a basis for evaluating treat-

ment. This applies, moreover, to some of our own cases, for if we used only cases having the signs recognized by Charcot, our list would be reduced by a half. Even our abstracted cases, used to illustrate the effects of vitamin E therapy, are not strictly in accord with an exact diagnosis as described in the original literature. We believe, however, that they satisfy the ordinary requirements of diagnosis in so complicated a field.

Peroneal Muscular Atrophy. The Charcot-Marie-Tooth form of muscular atrophy, peroneal muscular atrophy, is a somewhat different disease from progressive muscular atrophy, bulbar paralysis or amyotrophic lateral sclerosis. It is a heredofamilial disease with combined spinal cord and peripheral lesions. This syndrome, described in 1886, has some features of a system disease of the spinal cord and others linking it to the group of muscular dystrophies. Both the ventral horns and the peripheral nerves are involved. Because of muscular atrophy of all the muscles below the knee, followed by the intrinsic hand muscles, with fibrillations, the disease is one that vitamin E treatment might be expected to help. There is slight variation in the clinical forms of peroneal muscular atrophy but ordinarily the diagnosis is not questioned.

Discussion. In general, our report, like that of many others, indicates no beneficial results from the use of vitamin E in amyotrophic lateral sclerosis, progressive muscular atrophy, or peroneal muscular atrophy. Similar findings are reported by Fitzgerald and McArdle,⁵ Doyle and Merritt,³ Denker and Scheinman,² and others. The reports of Wechsler, on the other hand, and possibly those of Stone and of Gutiérrez-Mahoney,⁶ indicate a favorable influence of vitamin E on some of the intrinsic disease of the spinal cord and medulla. The discrepancies between these results cannot be explained at the present time. Further evidence will be needed before a final decision can be made. The weight of the reported cases, however, is against the value of vitamin E in the diseases under consideration.

It is hoped that the new method of studying the level of vitamin E in the blood, as reported by Wechsler and his coworkers,⁹ will be of value in separating out from any given group of patients those deficient in this vitamin. Although the details of the test have not been published, the preliminary report is disappointing, as far as amyotrophic lateral sclerosis is concerned. Untreated patients with this disease showed values within the normal range. Blood levels could be raised by oral administration of vitamin E, however, although patients thus treated did not all show clinical improvement.

Summary and Conclusions. Eleven patients with clinical amyotrophic lateral sclerosis, 6 with progressive muscular atrophy and 4 with peroneal muscular atrophy were treated with synthetic vitamin E, by mouth, over a period of 8 to 38 weeks.

Doses were progressively increased from 20 to 250 mg. per day by

mouth. In a few cases 50 mg. were added by intramuscular injection, 3 times a week.

In addition to vitamin E, most patients ingested vitamin B₁ complex, in various doses during the same period of observation.

No patient showed any permanent improvement; a few were subjectively better.

In general, the course of these diseases was not affected by the treatment; many were worse and some died during the period of observation.

Difficulties in exact diagnosis are commented upon as well as the importance of a quantitative test for the level of vitamin E in the blood.

Electromyograms are a convenient method of recording the number of fibrillations in an affected muscle. They do not, however, furnish a definite diagnostic clue to any of the diseases under consideration.

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DERMATITIS FROM TOPICAL APPLICATION OF 2-METHYL-1:4-NAPHTHOQUINONE (SYNTHETIC VITAMIN K ANALOGUE).

By R. C. PAGE, M.D.,

ASSISTANT PHYSICIAN TO DISPENSARY, NEW YORK POST-GRADUATE HOSPITAL; ASSOCIATE PHYSICIAN, VANDERBILT CLINIC, PRESBYTERIAN HOSPITAL; CLINICAL ASSISTANT PHYSICIAN, GRASSLANDS HOSPITAL, VALHALLA, N. Y.,

AND

Z. BERCOVITZ, M.D.,

ASSISTANT CLINICAL PROFESSOR OF MEDICINE, NEW YORK POST-GRADUATE MEDICAL SCHOOL OF COLUMBIA UNIVERSITY; ASSISTANT ATTENDING PHYSICIAN, NEW YORK POST-GRADUATE HOSPITAL, NEW YORK, N. Y.

(From the Gastroenterology Clinic, Department of Medicine, New York Post-Graduate Medical School and Hospital.)

THE increasing oral and parenteral use of 2-methyl-1:4-naphthoquinone for its vitamin K-like activity is good evidence that toxicity and untoward side effects of this substance are negligible in the therapeutic dose range by these routes. Our use of methylnaphthoquinone by topical application was suggested by the fact that it belongs to the group of fat-soluble vitamins (A, D, E and K) of which certain members are known to be absorbed through the skin.

Mackie, Eddy and Mills² have shown that defective absorption may be the cause of some of the vitamin A deficiencies occurring in

patients with colitis, and failure to respond to large oral doses of vitamin A was common. However, when cod-liver oil was given by inunction a prompt rise of blood vitamin A was usually obtained. de Beer, Drekter and Flusser¹ have shown that 2-methyl-1:4-naphthoquinone in suitable vehicles administered percutaneously to vitamin K deficient chicks will successfully cure them. A single dose of 1 γ per chick cured 50% of the depleted chicks and larger doses afforded protection for relatively long periods of time.

Because it has been shown that 2-methyl-1:4-naphthoquinone can be absorbed when applied to the unbroken skin of chicks,¹ it was decided to administer the drug by the percutaneous route to patients with chronic ulcerative colitis. An ointment containing 1% 2-methyl-1:4-naphthoquinone in a specially prepared base* was obtained and given to patients to apply by inunction to the skin. Each patient was given specific directions to rub the ointment over a different area of skin each night and allow it to remain overnight in order to obtain maximal absorption.

Nine adult patients were treated in this manner and the development of a dermatitis in 5 of them caused us to discontinue this method of administration (Table 1). We have not seen any reference to this phenomenon in the literature and the reporting of it seems opportune.

2-Methyl-1:4-naphthoquinone crystals (1 mg.) were applied to the skin of 3 normal persons, and in 24 hours an ulceration of the epithelium had occurred in 2 and a slight erythema had developed at the point of contact in the third person. Patch tests of the methylnaphthoquinone ointment were done on these 3 persons and an intense pruritus, erythema and edema of the area appeared in 1½ to 2 hours, followed in 24 hours by vesiculation. The skin which was in contact with the methylnaphthoquinone ointment subsequently turned a yellowish-orange color which persisted for a week. The pruritus was present for 3 to 4 days and tenderness of the area, similar to that occurring in actual burns, was present for 1 week. Patch tests of the ointment base were negative in all 3.

Discussion. The dermatitis from the methylnaphthoquinone ointment applied topically appeared to be due to the primary irritant effect of the chemical itself. Crystals of methylnaphthoquinone have been shown to be directly irritant to the epithelium. Apparently the dilution of the chemical (1%) by the ointment base caused a delay of several days in the appearance of the dermatitis. The patch tests of the methylnaphthoquinone ointment were inconclusive as they varied from negative to positive, in the persons who previously had a dermatitis. An individual variation in skin reaction to methylnaphthoquinone must be present, as the 3 normal persons patch-tested with the methylnaphthoquinone ointment gave a positive reaction. The subsequent inflammatory changes ran the course of a second-degree burn. The ointment base as a contribut-

* Supplied by Burroughs Wellcome & Co. (U. S. A.), Inc., New York, N. Y.

TABLE 1.—SYNOPSIS OF CASES.

Case.	Ointment containing 2-methyl-1:4-naphtho- quinone, 1%.		Dermal manifestations.	Total amount of MNQ* applied to skin (mg.).	Patch tests (performed following completion of ointment studies).		
	Quantity per single application (gm.).	Frequency of application.			Oint- ment MNQ,* 1%.	Oint- ment base.	Crystals, MNQ.*
1 L. C.	0.5	Daily for 7 days	None	95	—	—	
	No oint- ment	For 1 week	None				
	1	Daily for 6 days	Diffuse erythematous dermatitis with pruritus				
2 A. F.	0.5	Daily for 7 days	Pruritus, mild erythematous derma- titis, lasted several days	35	+	—	
3 R. M.	1	For 1 day	None	40	=	—	+ in 2 days
	No oint- ment	For 4 weeks	None				
	1	Daily for 3 days	Pruritus, erythema and edema of skin of abdomen, with an additional area on dorsum of right forearm; devel- oped into chr. eczematoid dermatitis				
4 M. P.	1	Twice in 1 week	None	40	—	—	+
	1	Only 1 day	None				
	No oint- ment	1 week	None				
	0.5	Daily for 2 days	Pruritus with a diffuse erythematous dermatitis				
5 M. T.	1	Daily for 3 days	Diffuse erythematous dermatitis	30			
6 M. C.	0.5	4 times in 1 week	None	20	+	—	+
7 F. K.	1	Daily for 1 week	None	70	—	—	+
8 E. R.	1	Every 3 da. for 4 ap- plications	None	40			
9 M. S.	1	Twice in 1 week	Skin burned after rubbing in ointment but no dermatitis appeared	55			
	No oint- ment	For 2 weeks					
	0.5	Daily for 1 week					

* Abbreviation for 2-methyl-1:4-naphthoquinone.

ing factor in the dermatitis can be ignored, inasmuch as patch tests were uniformly negative. From the results of this study it can be concluded that the percutaneous route of administration of methylnaphthoquinone is not a procedure of choice because of the occurrence of dermatitis in 5 of the 9 patients studied.

Methylnaphthoquinone in an ointment base has been applied percutaneously to newborn babies and has prevented the so-called physiologic hypoprothrombinemia of the newborn. In a series of 24 newborns in which this method was used no evidence of a contact dermatitis appeared.³

Summary. 1. Methylnaphthoquinone 1% in an ointment base applied to the skin of 9 patients resulted in a dermatitis in 5 of them.

2. The dermatitis appeared after several applications of the methylnaphthoquinone ointment and consisted in pruritus, erythema, edema of the skin, and in 1 case this went on to the appearance of a chronic eczematoid dermatitis.

3. Crystals of methylnaphthoquinone are primary irritants to the skin and the dilution of the methylnaphthoquinone by the ointment base results in a delayed appearance of the dermatitis.

4. Multiple topical application of methylnaphthoquinone in an ointment base does not appear to be a desirable procedure in adults. One or two applications did not cause any untoward side-effect.

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STUDIES OF THE B VITAMINS IN THE HUMAN SUBJECT.

V. THE NORMAL REQUIREMENT FOR THIAMINE; SOME FACTORS INFLUENCING ITS UTILIZATION AND EXCRETION:

By K. O'SHEA ELSOM, M.D.,

ASSOCIATE IN MEDICINE, UNIVERSITY OF PENNSYLVANIA MEDICAL SCHOOL; RESEARCH FELLOW, PHILADELPHIA GENERAL HOSPITAL,

JOHN G. REINHOLD, Ph.D.,

BIOCHEMIST, PHILADELPHIA GENERAL HOSPITAL,

JOSEPH T. L. NICHOLSON, M.D.,

HAWLEY-THOMPSON FELLOW IN GASTROENTEROLOGY AND ASSISTANT INSTRUCTOR IN MEDICINE, UNIVERSITY OF PENNSYLVANIA MEDICAL SCHOOL; RESEARCH FELLOW, PHILADELPHIA GENERAL HOSPITAL,

AND

CHARLOTTE CHORNOCK, Ph.D.,

RESEARCH CHEMIST, PHILADELPHIA GENERAL HOSPITAL,
PHILADELPHIA, PA.

(From the Thompson Vitamin Clinic of the Philadelphia General Hospital and of the Kinsey-Thomas Foundation of the University of Pennsylvania Medical School.)

A KNOWLEDGE of the minimal human requirement for thiamine, as well as for other members of the B complex, is essential in order to assess the adequacy in that respect of any diet or to determine

when supplementation of the diet is indicated. Recent studies have attempted to fix the normal range of the need for thiamine¹⁵ and for riboflavin¹³ in the human being, but no effort has been made to assess the factors which determine it. Cowgill originally proposed that the requirement depends on the body weight and the total caloric intake.³ Although indirect confirmation of the accuracy of his formula has been possible,^{4,9} in no instance has its applicability to man been put to direct test. Accordingly, the present observations were carried out to determine whether the minimal requirement for thiamine is accurately expressed by the Cowgill formula and to evaluate in a preliminary fashion the rôle of body weight and of caloric intake in determining that requirement.

Further knowledge is also needed of factors which determine the urinary excretion of thiamine in the normal subject, since that has been used as a measure of deficiency.^{1,11,14} Accordingly, the factors of body weight, total caloric intake, infection, and, in 3 subjects, the development of deficiency, have been studied for their influence on the urinary excretion of thiamine.

TABLE 1.—ARTICLES COMPOSING THE EXPERIMENTAL DIET.

Breakfast.	Lunch.	Supper.
Orange juice	Lamb, beef, or chicken	Rice
Cream of wheat	Potato	Cheese, American
Milk	Spinach, carrots or string	Bread
Egg	beans	Butter
Bacon	Bread	Pear, pineapple, peach
Toast	Butter	Lettuce
Butter	Cornstarch pudding	Olive oil
Jelly		Sugar
		Candy
		Gelatine

Methods of Study. Six women, without complicating disease,* or pre-existing evidence of deficiency, served voluntarily as subjects for this study. They resided in our Vitamin Ward,† where they consumed a constant daily quantity of an experimental diet for 28 to 120 days (Table 1). Weighed separately for each subject, the diet supplied daily a specific amount of thiamine‡ slightly in excess of the theoretical requirement as calculated

* Two of the subjects (A. H. and F. P.) showed clinical and laboratory evidence of chronic hepatic disease. We could, however, obtain no indication¹⁰ that their utilization of the B vitamins differed from normal at the levels of intake here employed. Hence, for the purposes of the present study they are included as essentially normal subjects.

† The ward of the Thompson Vitamin Clinic contains 8 beds and is devoted solely to the study of vitamin deficiencies. It is operated as a separate unit so that the subjects may be kept under the constant 24-hour supervision of a staff of 4 graduate nurses and so that rigid control of the food and fluid intake and of the collection of urine and feces may be maintained. The subjects, selected for their willingness to cooperate and for their lack of conflicting disease, are confined to the ward and an adjoining sundeck so that environmental conditions are essentially constant. Special recreational procedures and occupational therapy are provided.

‡ The thiamine content of individual foods was calculated from the Cowgill tables.³ The total daily thiamine intake was measured by chemical analysis of the total food consumed by 1 subject on 3 different days. Close agreement was found between calculated and actual intake.

by the Cowgill formula.* A second group of 3 women, likewise resident in the Vitamin Ward consumed essentially the same foods† but in amounts which supplied approximately one-half of their requirement. The protein, fat, carbohydrate and the total calories of the diet were adequate for each individual. Ascorbic acid,‡ and in certain instances vitamins A and D § and also calcium, were given as supplements. Additional quantities of other members of the B complex were not given since their influence on the utilization of thiamine is not at present understood and hence it seemed more desirable to study the behavior of thiamine when all the B factors were reduced more or less proportionately. The dietary conditions so established thus resembled more nearly those actually encountered in clinical deficiencies in which the supply of the entire B complex is likely to be reduced.

The subjects were weighed daily under standard conditions and were observed closely for the development of symptoms and physical signs of deficiency. Activity from day to day was essentially constant for each subject. The basal metabolic rate and urea clearance were normal in every instance. Fluid intake was maintained at 1500 ml. daily. The urine excreted over each 24 hours was collected in brown glass bottles containing 10 ml. of glacial acetic acid and was kept in a refrigerator until assayed. The output of thiamine for each 24 hours was determined separately.

The thiamine** content of both food and urine were determined by an adaptation of the thiochrome method of Hennessy and Cerecedo,⁷ as modified in the laboratories of Merck & Co., Inc.^{6††} A fluorometer constructed on the principles outlined by Cohen² and incorporating suggestions made by Hills⁸ was used. The source of ultraviolet light was a 100-watt Type H General Electric lamp. The incident light was filtered through Woods glass. A Type II Western Photronic cell, screened by a Wratten 2A filter, was employed to measure fluorescence, the current from the photocell being measured by means of a Rubicon high-sensitivity galvanometer. Solutions of thiamine analyzed simultaneously with unknowns were used as standards for fluorometry. Thiamine added to urine was recovered within $\pm 10\%$ of the theoretical, although usually deviations were much smaller.

In the food analyses an amount exactly equal to that consumed by an individual in a given day was finely ground and was extracted overnight with 3 liters of 3% sulphuric acid. The extract was then thoroughly shaken and 100 ml. aliquots containing approximately 0.5 to 3.2 $\mu\text{g.}$ of thiamine were autoclaved and assayed in duplicate for free and total thiamine using standard thiamine solutions for comparison. The duplicate determinations agreed closely.

Results. *The Normal Requirement for Thiamine.* Of the 6 women who received a daily amount of thiamine closely approximating the theoretical requirement as calculated by the Cowgill formula, the

$$* \frac{\text{Vitamin B}_1 \text{ (micrograms)}}{\text{Calories}} = 0.0000284 \text{ weight} \times 0.166. \\ \text{grams}$$

† Orange juice, egg and bacon were the only articles of food omitted in the deficient diet.

‡ The ascorbic acid was kindly supplied by E. R. Squibb & Sons, New York City.

§ Vitamins A and D were generously supplied as Cod Liver Oil Concentrate Capsules by Dr. E. R. Neary, The White Laboratories, Inc., Newark, N. J.

** We are indebted to Merck & Co., Rahway, N. J., for generous supplies of thiamine, as "Betabion," used throughout these studies.

†† We are indebted to Dr. William L. Sampson for advice concerning the application of the thiochrome method.

ratio Thiamine varied from 1.03 to 1.1 (Table 2).
 Theoretical requirement
 Thus if the requirement were as indicated by the Cowgill formula all should have remained well. Actually, however, 3 subjects developed clinical manifestations of deficiency, whereas, during the same period, the other 3 subjects remained well. Those who developed evidence of deficiency had received, because of their small body weight, the smallest amounts of thiamine on the basis of the Cowgill formula. This suggests that body weight may be disproportionately represented in the formula, which therefore does not accurately predict the thiamine requirement of smaller individuals.

TABLE 2.—DATA RELATIVE TO THEORETICAL REQUIREMENT, INTAKE AND URINARY EXCRETION OF THIAMINE.

Subject.	Days on diet.	Body weight, pounds.	Calories.	Requirement by Cowgill formula, μ g.	Daily intake, μ g.	Thiamine.			Average daily excretion, μ g.
						Theoretical requirement.	Weight.	Calorie.	
E. V.*	63	108.8	1752	398	204	0.51	1.88	0.12	21
A. B.*	37	108.5	1711	398	204	0.51	1.88	0.12	32
R. A.*	77	202.3	2082	825	353	0.43	1.74	0.17	35
M. H.†	36	95.5	1608	380	413	1.09	4.32	0.25	34
A. T.†	28	129.5	1784	503	519	1.03	4.00	0.28	32
I. C.†	120	127.5	2049	524	574	1.10	4.50	0.28	42
A. H.‡	36	143.5	1860	610	651	1.07	4.54	0.35	46
J. Z.‡	28	156.8	2019	646	703	1.09	4.48	0.35	58
F. P.‡	36	169.0	1943	715	773	1.08	4.58	0.40	60

* Definite deficiency.

† Early deficiency, except I. C. who developed definite deficiency after infection.

‡ No deficiency.

Because of the limited number of subjects it is not possible to exclude altogether the possibility of a chance occurrence of deficiency in the smaller members of the group. Further experimentation is therefore required to establish the part played by body weight in determining the requirement for thiamine, but our observations strongly suggest that its influence is less important than implied in Cowgill's formula.

The absolute thiamine intake and the thiamine/calorie ratio were higher in all of our subjects without deficiency than in those who developed it, whereas no clear division between those with deficiency and those with no deficiency was apparent on the basis of the thiamine/weight ratio. The minimal absolute thiamine intake compatible with health was about 651 μ g., and the thiamine/calorie ratio about 0.35. Which of these factors constitutes the better basis for the prediction of the normal requirement must be determined by further clinical study.

It should be pointed out that, with the exception of Subject I. C., these observations were made over a comparatively short period, and the minimal amounts of thiamine given above may be inadequate for subsistence over a longer time.

Daily Variation in Urinary Excretion of Thiamine. The amount of thiamine excreted varied appreciably from day to day, independently of the urine volume. The absolute variation in thiamine excretion was approximately proportional to the magnitude of the intake (Table 3). The amount excreted for each subject remained within a characteristic range from the beginning to the end of observation (Chart 1). Variations within this range were not associated with any obvious change in the subject's condition. There was no change in output, for example, during menstruation. These facts suggest that the daily variations in excretion did not represent true differences in utilization but were related to factors governing the absorption or excretion of the vitamin.

TABLE 3.—VARIATION IN URINARY EXCRETION OF THIAMINE ON A CONSTANT INTAKE.

Subject.	Daily intake, μg.	Urinary thiamine.		
		Average daily output, μg.	Standard deviation (σ).	Coefficient of variation, %
E. V.*	204	21	5.6	26.6
A. B.*	204	32	4.8	15.0
R. A.*	353	33	11.1	33.5
M. H.†	413	34	9.6	28.0
A. T.†	519	32	7.3	23.0
I. C.†	574	42	11.7	28.0
A. H.‡	651	56	15.0	27.0
J. Z.‡	703	58	16.2	28.0
F. P.‡	773	60	24.6	41.0

* Definite deficiency.

† Early deficiency except I. C. (see text).

‡ No deficiency

$$\% \text{ Coefficient of variation} = \frac{\text{Standard deviation} \times 100}{\text{Mean}}$$

Relation of Urinary Excretion to Body Weight and Caloric Intake. The output of thiamine varied directly with the intake and was independent of body weight in all of the subjects studied (Table 2). A striking illustration of this fact is provided by the 2 subjects who represented the extremes in body weight. Thus Subject R. A., weighing 202.3 pounds, who took a deficient diet, received an amount of thiamine comparable to that consumed by Subject M. H. who weighed 95.5 pounds. Both subjects excreted the same average daily quantity of thiamine. If body weight were a major factor in determining the output of thiamine the excretion in these 2 subjects should have differed widely.

A further demonstration of the direct relationship between intake and output regardless of body weight is provided by statistical analysis of the urinary excretion figures of the group who received daily amounts of thiamine just sufficient to meet their theoretical requirement. In this group intake increased in proportion to both body weight and calories since it was determined on the basis of the Cow-

gill formula. However, by means of the partial correlation technique* it was possible to analyze these factors separately as a result of which a highly significant correlation was demonstrated between intake and output (Table 4), while no correlation could be demonstrated between output and body weight or caloric intake.

TABLE 4.—PARTIAL CORRELATIONS BETWEEN OUTPUT OF THIAMINE AND INTAKE, BODY WEIGHT AND CALORIES.

Correlations.	Coefficient of correlation (r).†	Probability of chance correlation (P).‡	Correlation.
Intake with output, body weight constant	+0.921	<0.01	Highly significant
Body weight with output, intake constant	+0.250	>0.50	None
Calories with output, intake constant	+0.379	>0.10	None

Urinary Excretion of Thiamine During Infection. Acute tonsillitis developed in 1 subject (I. C.) and was accompanied by a significant decrease in the average daily output of thiamine (Table 5). Fever was present for only 3 days at the outset, but evidence of infection persisted for a total of 15 days. The excretion of thiamine remained

TABLE 5.—URINARY EXCRETION OF THIAMINE DURING INFECTION (SUBJECT I. C.).

Date, 1940-1941.	Days.	Average daily urinary thiamine, µg.	Clinical condition.	Significance of the differences between averages (P).§
11/ 5-12/15	41	(A) 50	Normal	
12/16-12/30	15	(B) 32	Infection; no manifestations of deficiency	(A) - (B) <0.01
12/31- 2/ 4	36	(C) 43	No infection; early manifestations of deficiency	(B) - (C) <0.01

low during this entire period despite unchanged intake, but, coincident with recovery, returned to normal. These findings suggest that there may have existed during the illness increased utilization of thiamine, that this was not limited to the period of pyrexia and that it terminated with recovery. This subject developed clinical evidence of deficiency immediately following the period of infection

* By utilizing the partial correlation technique:

$$r_{12.3} = \frac{r_{12} - r_{13} \times r_{23}}{\sqrt{1 - r_{13}^2} \sqrt{1 - r_{23}^2}}$$

it is possible to determine the relationship between two factors independently of the possible effect of variations in the third.

† Correlations of 0.9 and above indicate a close correlation between two measurements. The highest possible correlation is 1.0. Correlations below 0.4 indicate very little relationship.

‡ P = the probability that the observed difference might have occurred by chance. When P is 1.0 the difference is a purely chance affair. If P is 0.05 there are only 5 chances out of 100 that the difference could have occurred by chance. As the value of P decreases the likelihood increases that a difference in the observed direction will be consistently found.

§ For definition of P see Table 4.

making it appear probable that her intake of thiamine was barely adequate prior to infection and was rendered inadequate by the increased demand for thiamine during this period.

Urinary Excretion of Thiamine in Relation to Clinical Deficiency. The 3 subjects who subsisted at approximately one-half of their theoretical requirement for thiamine first showed the characteristic manifestations of deficiency^{4,5} on the 23d, 32d, and 41st day after beginning the diet. These signs slowly increased in severity until thiamine was administered. In none was the appearance or further development of clinical evidence of deficiency associated with altered output of thiamine (Table 6). Very soon after the diet was begun, the daily thiamine excretion in the urine reached a level and did not vary significantly therefore (Chart 1).

TABLE 6.—URINARY EXCRETION OF THIAMINE BEFORE AND DURING DEFICIENCY.

Subject.	Theoretical requirement for thiamine, $\mu\text{G.}$	Daily intake of thiamine,* $\mu\text{G.}$	Average daily urinary thiamine.		
			Before deficiency, $\mu\text{G.}$	During early deficiency, $\mu\text{G.}$	During definite deficiency, $\mu\text{G.}$
R. A. . . .	825	353	35 (23 days)	29 (37 days)	37 (17 days)
A. B. . . .	398	204	32 (32 days)	..	31 (6 days)
E. V. . . .	398	204	21 (41 days)	21 (15 days)	25 (7 days)

* Before beginning the deficient diet the intake of thiamine was as follows: R. A. an average of 677 $\mu\text{g.}$ daily for 11 days; A. B. 100 $\mu\text{g.}$ daily in addition to 204 $\mu\text{g.}$ of thiamine in the diet for 35 days; E. V. an average of 821 $\mu\text{g.}$ for 15 days.

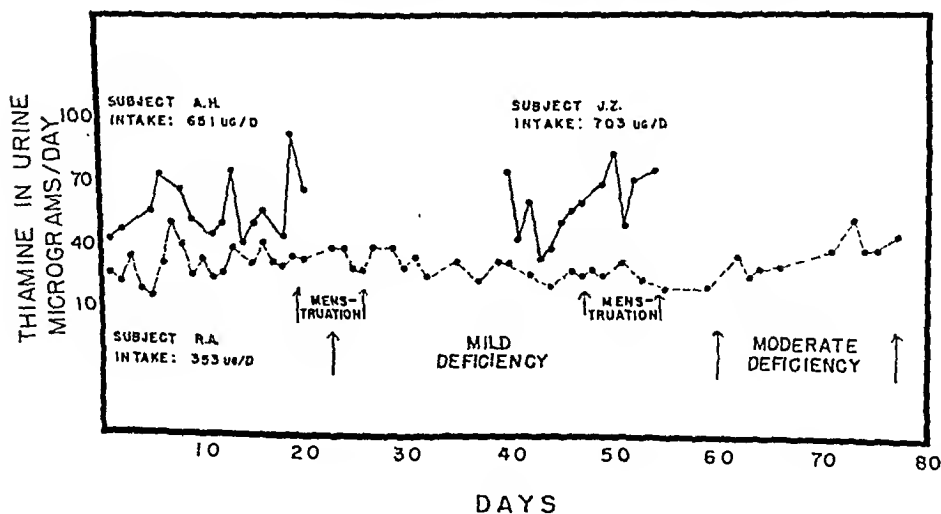


CHART 1.—Daily urinary excretion of thiamine in 3 subjects taking the experimental diet. Broken line shows observation on Subject R. A. who consumed a diet deficient in the B complex and who after 23 days first showed clinical manifestations of deficiency; solid lines show observation on Subjects A. H. and J. Z. who received a diet adequate in B complex.

Thus the excretion of thiamine appears to be influenced mainly by factors which determine its concentration in blood and tissues

(daily intake, infection, proportion of dietary elements¹²) rather than by the altered function resulting from its reduction in the diet. In view of these facts it may be assumed that factors which lower the excretion of thiamine likewise result in reduction of the amount of thiamine available to the tissues and the amount in the urine, therefore, may be considered as an indication of the immediate available supply of the vitamin. It cannot be said, however, that because the excretion of thiamine is reduced, altered function due to thiamine deficiency has resulted. For this reason the usefulness of the measurement of thiamine output in the urine as an indication of the presence or absence of deficiency appears to be limited.

These observations also suggest that there had been very little storage of thiamine since no significant difference in the time of onset of clinical deficiency in the 3 subjects was observed although their previous intake of thiamine had been strikingly different (Table 6). Furthermore, if the thiamine in the deficient diet had been augmented by stores from the tissues, the excretion in the early stages of deficiency should have exceeded that in the later period.

Summary. 1. Six subjects, without previous evidence of deficiency, subsisted on a constant daily diet containing thiamine in amounts just sufficient to meet the theoretical requirement as calculated by the Cowgill formula. Three other subjects received the same diet in amounts which supplied approximately one-half of the theoretical requirement for this vitamin.

2. Of the 6 subjects who received the theoretically required amount of thiamine, 3 developed deficiency and 3 did not. Those who developed deficiency were the smaller members of the group. Thus the Cowgill formula failed adequately to predict the normal requirement for thiamine, probably through too great emphasis on body weight.

3. The minimal adequate intake of thiamine for this group was about 651 μ g. per day, the thiamine/calorie ratio about 0.35.

4. The amount of thiamine in the urine varied from day to day, the absolute variation being approximately proportional to the magnitude of the intake.

5. The output of thiamine in the urine was directly correlated with the intake. No relationship was demonstrated between the output of thiamine and body weight or calorie intake.

6. The output of thiamine in the urine was lowered in 1 case in the presence of infection and returned to normal when the infection subsided.

7. The development of clinical deficiency did not alter the output of thiamine in the urine.

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A COMPARISON OF THE BACTERIOSTATIC EFFECT OF THE SULFONAMIDE DRUGS UPON THE GROWTH OF 25 STRAINS OF STREPTOCOCCUS VIRIDANS.

By MARY A. POSTON, M.A.,

INSTRUCTOR IN BACTERIOLOGY, DUKE UNIVERSITY SCHOOL OF MEDICINE; ASSISTANT
BACTERIOLOGIST, DUKE HOSPITAL,
AND

EDWARD S. ORGAIN, M.D.,

ASSOCIATE IN MEDICINE, DUKE UNIVERSITY SCHOOL OF MEDICINE; ASSISTANT PHYSICIAN,
DUKE HOSPITAL, DURHAM, N. C.

(From the Departments of Bacteriology and Medicine, Duke University School of
Medicine and Duke Hospital.)

In a previous communication, we reported a series of experiments showing the bacteriostatic effect *in vitro* of sulfanilamide and five of its related compounds upon various organisms isolated from human cases of bacterial endocarditis.⁵ This series included 14 strains of *Strep. viridans*. Little work has been reported demonstrating the effectiveness *in vitro* of the sulfonamide drugs upon this group of organisms.^{1,2,3,6} Since new compounds have become available, it seemed of sufficient importance to warrant a report of the results of experiments *in vitro* showing the inhibitory power of three new sulfonamide drugs, and four of the previous ones, upon the 14 strains formerly used and an additional 11 strains of *Strep. viridans*.

Materials and Methods. All of the strains of *Strep. viridans* were isolated from the blood of 25 patients who had had consistently positive blood cultures. The clinical diagnosis of 20 of these patients was bacterial endocarditis, 2 patients had acute rheumatic fever, and there was 1 case each of rheumatoid arthritis, carcinoma of the stomach and Boeck's sarcoid. Within 48 hours after isolation, the organisms were lyophilized to preserve their original characteristics until the time of the experiment.

Sulfanilamide, sulfapyridine, sodium sulfapyridine, sulfathiazole, sodium sulfathiazole, sulfadiazine and sodium sulfadiazine were chosen for the

experiments. Because of differences in the solubilities* of these drugs in broth and because it was desired to use concentrations of drug comparable to the concentrations obtainable in the blood by therapeutic administration, they were divided into two groups. Sulfanilamide and the sodium salts were tested in concentrations of 30, 25, 20, 15, 10 and 5 mg. per 100 cc. The other drugs were used in concentrations of 10, 7.5, 5 and 2.5 mg. per 100 cc.

The concentrations of sulfanilamide and the sodium salts were prepared by suitable dilutions of a stock solution containing 0.1% of the drug in beef infusion bacto-peptone (buffered) broth, pH 7.4. The stock solutions were sterilized by filtration through a Seitz filter pad and the concentrations were checked by chemical determinations.† The other drugs were prepared from stock solutions containing 0.01% of the drug in the same buffered broth. The pH of the broth was checked after the drugs were added and again at the end of the experiment. There was no appreciable difference between the pH of the broth containing the sodium salts and that containing the other drugs.

Five test tubes containing 10 cc. of each concentration of drug were inoculated with 0.1 cc. of a suspension of a 24-hour broth culture diluted to contain 1000 organisms per cc., making the concentration at the beginning of the experiment 100 organisms per cc. Ten control tubes containing no drug were inoculated at the same time. Readings of the photoreflexometer (Libby) were taken after 24 hours' incubation. After the readings of the photoreflexometer were taken, 0.1 cc. amounts were transferred from the tubes showing no growth to tubes containing 10 cc. cooled molten agar to which 1 cc. of sterile blood had been added and plates were poured. In every instance these plates were sterile. The results of the experiments are given in the tables.

Discussion. The data in Table 1 show the great variation in the effectiveness *in vitro* of the sulfonamide drugs on a large number of strains of a single species of bacteria, *Strep. viridans*. Of a total of 25 strains, the growth of 17 strains of *Strep. viridans* was inhibited by one or more drugs. In this series, the growth of 3 strains was inhibited significantly by all seven drugs, in contrast to 7 strains whose growth was not inhibited by any of the drugs. The remaining 14 strains showed considerable variation. The growth of 5 strains was inhibited by five drugs, 3 strains by four drugs, 2 strains by two drugs and the growth of 1 strain was inhibited by only one drug. With one exception (A. B.), no drug was bacteriostatic unless sodium sulfapyridine was effective also. This strain (A. B.) was isolated from a patient with bacterial endocarditis, who had been treated previously with sulfapyridine.

The summary of the relative bacteriostatic effects of each of these drugs is given in Table 2. Sodium sulfapyridine exhibited the most marked effectiveness on the greatest number of strains.

* The sodium salts were used so that higher concentrations of the drugs could be obtained. Since the same concentrations of drugs and their sodium salts were not comparable in their inhibiting effects, the data of experiments using both forms of the drugs are given in the tables. No explanation of the discrepancy can be given at the present time, although it has been noted in numerous experiments.

† The determinations were performed by Miss Sara Bunch of the Department of Biochemistry, Duke Hospital, Durham, N. C.

TABLE 1.—EFFECTIVENESS OF VARIOUS SULFONAMIDE COMPOUNDS ON 25 STRAINS OF *STREP. VIRIDANS*.

Strain.	Sodium sulfapyridine.	Sulfanilamide.	Sulfapyridine.	Sulfathiazole.	Sodium sulfathiazole.	Sulfadiazine.	Sodium sulfadiazine.
A. C. . .	++	++	++	++	++	++	++
H. W. . .	++	++	+	++	++	++	++
F. C. . .	++	++	0	+	++	0	0
L. C. . .	++	++	+	0	0	0	0
B. McG. . .	++	++	+	0	0	0	0
O. C. . .	++	+	0	+	++	+	++
N. S. . .	++	+	+	+	++	+	+
C. Y. . .	++	+	0	0	0	0	0
P. D. . .	++	0	+	+	++	+	++
H. S. . .	++	0	+	++	++	+	++
C. W. . .	++	0	+	+	++	++	++
A. S. . .	++	0	+	+	++	++	++
J. C. . .	++	0	0	0	0	0	0
W. P. . .	+	+	+	+	++	0	0
L. A. . .	+	+	0	+	+	0	0
O. E. . .	+	+	0	0	0	0	0
A. B. . .	0	0	0	+	+	+	++
S. W. . .	0	0	0	0	0	0	0
E. B. . .	0	0	0	0	0	0	0
W. F. . .	0	0	0	0	0	0	0
E. Me. . .	0	0	0	0	0	0	0
D. B. . .	0	0	0	0	0	0	0
B. G. . .	0	0	0	0	0	0	0
E. O. . .	0	0	0	0	0	0	0
J. B. . .	0	0	0	0	0	0	0

++ = No growth in 24 hours in concentrations of 20 mg. per 100 cc. or less of sulfanilamide, sodium sulfapyridine, sodium sulfathiazole, sodium sulfadiazine and 5 mg. per 100 cc. or less of the other drugs.

+ = No growth in 24 hours in concentrations of 25 or 30 mg. per 100 cc. of sulfanilamide, sodium sulfapyridine, sodium sulfathiazole, sodium sulfadiazine and 7.5 or 10 mg. per 100 cc. of the other drugs.

0 = No inhibition of growth in concentrations of the drugs used in the experiment.

TABLE 2.—EFFECTIVENESS OF VARIOUS SULFONAMIDE COMPOUNDS ON 25 STRAINS OF *STREP. VIRIDANS*.

Drugs.	Inhibition of growth.						No inhibition of growth.	
	Complete.		Partial.		Total.			
	No.	%.	No.	%.	No.	%.	No.	%.
Sodium sulfapyridine . . .	13	52	3	12	16	64	9	36
Sulfanilamide . . .	6	24	9	36	15	60	10	40
Sodium sulfathiazole . . .	11	44	3	12	14	56	11	44
Sodium sulfadiazine . . .	8	32	4	16	12	48	13	52
Sulfathiazole . . .	3	12	8	32	11	44	14	56
Sulfapyridine . . .	2	8	8	32	10	40	15	60
Sulfadiazine . . .	4	16	5	20	9	36	16	64

Complete inhibition of growth: No growth after 24 hours in concentrations of 20 mg. per 100 cc. or less of sulfanilamide, sodium sulfapyridine, sodium sulfathiazole, sodium sulfadiazine and 5 mg. per 100 cc. or less of the other drugs.

Partial inhibition of growth: No growth after 24 hours in concentrations of 25 or 30 mg. per 100 cc. of sulfanilamide, sodium sulfapyridine, sodium sulfathiazole, sodium sulfadiazine and 7.5 or 10 mg. per 100 cc. of the other drugs, or some degree of inhibition in lower concentrations.

No inhibition of growth: No inhibition of growth in any concentration of the drugs used in the experiment.

Because of the great variation in the effectiveness *in vitro* of sulfanilamide and its related compounds on *Strep. viridans*, it is

important to test the bacteriostatic effect in the test tube of the various sulfonamides on the organism before the institution of chemotherapy, in patients suffering from bacterial endocarditis. It has been shown that there is a definite correlation between the growth-inhibiting concentration in the test tube and the therapeutic effectiveness of comparable concentrations in the patient's blood.⁴

If preliminary experiments *in vitro* are impossible, these experiments would indicate that sodium sulfapyridine is the probable drug of choice, since it effectively inhibits the greatest number of strains.

Conclusions. 1. The bacteriostatic effects of sulfanilamide, sulfapyridine, sodium sulfapyridine, sulfathiazole, sodium sulfathiazole, sulfadiazine and sodium sulfadiazine upon the growth of 25 strains of *Strep. viridans*, isolated from the blood of patients, have been studied.

2. The results indicate not only a great variation in the effectiveness of these drugs against a large number of strains of a single species of bacteria, but also a great variation in the susceptibility of each strain to various drugs.

3. In this series, sodium sulfapyridine exhibited the most marked effectiveness against the greatest number of strains.

We wish to express our appreciation to Drs. D. T. Smith and D. S. Martin for their suggestions and help in the preparation of this paper, and to Lederle Laboratories, Inc., New York, N. Y., for furnishing us with the sodium sulfathiazole, sulfadiazine and sodium sulfadiazine used in these experiments.

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AN EVALUATION OF IONTOPHORESIS USING DIFFERENT VASODILATING DRUGS FOR TREATMENT OF RHEUMATOID ARTHRITIS.

BY CHARLEY J. SMYTH, M.D.,

AND

R. H. FREYBERG, M.D.,

ANN ARBOR, MICH.

(From the Rackham Arthritis Research Unit,* the Medical School, University of Michigan.)

THE treatment of arthritis by iontophoresis, or cataphoresis, is a comparatively recent therapeutic procedure whereby vasodilating drugs are introduced through the skin about the affected joints by

* This unit is supported by the Horace H. Rackham School of Graduate Studies, of the University of Michigan.

means of galvanic current. Histamine and acetyl- β methylcholine chloride have been the drugs commonly used by iontophoresis in the treatment of rheumatic diseases. The rationale for their use is the relief of vascular spasm and the resultant decreased peripheral circulation, which some investigators consider to be important factors in initiating and maintaining chronic arthritis. This method of therapy has been steadily increasing in popularity and although opinions differ somewhat concerning its usefulness, there have been numerous reports of its advantages.^{1-4,5a,6a,b,7} With few exceptions previous studies have been uncontrolled, have lacked adequate classification of the diseases treated, and have been based upon short-term observations. The purpose of this investigation was to critically evaluate iontophoresis, using different vasodilating drugs in the treatment of patients with rheumatoid arthritis.

Methods. Twenty-eight patients, 15 males and 13 females, having characteristic rheumatoid arthritis as established by history, physical examination, roentgenograms and an elevated erythrocyte sedimentation rate, were selected for this study. In most cases, paired joints were affected to an equal degree. This allowed excellent control of this investigation; one of the pair of comparably diseased joints was treated with one vasodilating drug while its mate was left untreated or was treated by another vasodilating drug or by another method of physical therapy. The duration of observation after completing the series of treatments averaged 9 months, in some cases it was as long as 22 months. A follow-up period of this length is adequate to indicate whether this form of therapy has more than temporary effects. The duration of the disease and the activity of the inflammation at the time of treatment varied considerably. No type of special therapy, such as gold salts, vaccines, sulphur or large doses of vitamin D, were given to these patients during the time that they were treated by iontophoresis.

All treatments were given by the same technician using the same galvanic machine. Patients were placed in the recumbent position and protected from chilling and draft. The parts treated were shaved, if necessary, and then washed with soap and water. Usually two, occasionally three, and never more than four, joints were treated at the same time. The joints were treated daily or on alternate days. In some cases a series of daily treatments were given and later, after an interval of 2 to 4 weeks, another similar series was given.

Three different drugs were employed: acetyl- β -methylcholine chloride (mecholy) 1:500 aqueous solution, histamine phosphate 1:1000 aqueous solution, and histamine dihydrochloride in an ointment base (*imadyl unction**). When the solutions were used, fabricated asbestos pads were saturated with the drug and wrapped snugly about the joint, without the patient knowing which drug was being employed. The histamine unction was applied directly to the skin over the joint without rubbing and was covered by a saline moistened fabricated asbestos pad fitted closely to the skin. Outside of the asbestos pad a thin lead strip was wound and this was connected to the positive pole of the galvanic machine. The asbestos pad and the lead strip electrode were held tightly in place by an elastic bandage. The large negative dispersive electrode was placed under the buttocks. The duration of each treatment varied usually between 20 and 30 minutes. The current was gradually increased until it reached a strength

* *Imadyl unction* contains acetyl-glycol-salicylic ester 5%, histamine dihydrochloride 1%, methyl salicylate, menthol, and thymol in an ointment base. It was supplied through the courtesy of Hoffmann La Roche, Inc., Nutley, N. J.

TABLE 1.—RESULTS OF IONTOPHORESIS TREATMENT GIVEN ON THE SAME DAYS TO COMPARABLY DISEASED JOINTS BUT EMPLOYING DIFFERENT VASODILATING DRUGS AT DIFFERENT JOINTS TREATED.

Case No.	Age and sex.	Duration of disease (yrs.).	Activity of disease (grade*).	Joints treated.	Drugs used.	No. of treatments (total).	Joints treated by other physical therapy or untreated.	Period of follow-up (mos.).	Results of therapy.
1	28 M	7	II	Lt. ankle Rt. ankle Rt. ankle†	Imadyl Meecholy Imadyl	6 8 14	12	Subj.: mod. improv. equal in both ankles; local sweating lasts 10 hrs. Obj.: none; all symp. rel. to pre-treatment degree 5 wks. later.
2	56 F	5	III	Rt. knee Lt. knee Rt. knee Lt. knee Rt. knee Lt. knee Rt. knee Lt. knee	Meecholy Imadyl Imadyl Histamine phosphate Imadyl	27 27 8 3 28 66	2	Subj.: mod. immed. relief of pain equal with each drug lasting 6 to 8 hrs.; no diff. between drugs. Obj.: Cutan. burn with imadyl. Marked uncomfortable flush with histamine phosphate.
3	53 F	21	II	Rt. elbow† Rt. wrist Rt. hand Rt. knee Lt. elbow† Lt. wrist Lt. hand Lt. knee	Meecholy Imadyl	7 6 13	13	Subj.: sl. red. in pain and stiffness, equal on both sides; meecholy caused sl. more generalized flush. Obj.: none.
4	51 M	3	IV	Rt. elbow Lt. knee Lt. elbow Lt. knee Lt. elbow Lt. knee	Meecholy Imadyl Histamine phosphate	32 18 14 62	4	Subj.: all 3 drugs prod. sl. benefit lasting less than 24 hours. Obj.: patches of urticaria with imadyl; marked generalized flush with histamine phosphate; no lasting benefit.
5	54 M	3	III	Rt. knee Lt. knee Rt. elbow Rt. wrist Lt. elbow Lt. wrist	Meecholy Imadyl Meecholy Imadyl	7 7 9 9 16	12	Subj.: mod. improv. in all joints, similar with each drug. Obj.: none.

6	52 M	20	I	Rt. elbow Lt. elbow	Meecholy Imadyl	17 17	17	10	Subj.: mod. less pain with meecholy, sl. less with imadyl; patient pre- ferred meecholy to imadyl; temp. relief only. Obj.: marked hyperemia with meech- oly, mod. hyperemia with imadyl.
7	21 F	11	II	Rt. knee Lt. knee Lt. knee	Imadyl Histamine phosphate Meecholy	4 4 7	11	11	Subj.: mod. red. in pain and stiffness lasting 2 hrs. with imadyl; intense pruritus with hist. phosph. was ob- jectionable. Obj.: none.
8	58 M	4	I	Rt. knee Rt. ankle Lt. knee Lt. ankle	Meecholy Meecholy Imadyl	28 6 6	34	22	Subj.: iner. local heat lasting 4 to 6 hrs. with each drug; mod. benefit. Obj.: none; benefit lasted for 2 mos. then all previous symptoms ret. to same degree.
9†	32 F	5	II	Rt. elbow Rt. wrist Rt. foot	Meecholy Imadyl Meecholy	22 4 6		9	Subj.: sl. red. in swelling and sl. iner. in motion in joints treated by ionto- phoresis only. Obj.: none.
10§	60 M	1	III	Rt. wrist and knee	Meecholy Histamine phosphate Imadyl	7 4 19		17	Subj.: mod. relief of pain lasting 2 wks. in joints treated by iontophoresis; no impr. in joints treated with Roentgen ray. Obj.: none.
12§	62 M	2	II	Both knees	Histamine phosphate Imadyl	7 7		6	Subj.: marked immed. relief of pain in all joints treated equal with ionto- phoresis and Roentgen ray; "place- bo" Roentgen irradiation equally effective. ¶
13§	50 M	6	II		Meecholy Imadyl Meecholy Histamine phosphate	16 9 15 6		‡	Subj.: mod. red. in pain with ionto- phoresis; no impr. following Roent- gen ray. Obj.: none.

* Inflammatory process is graded I to IV to indicate increasing activity of the disease.

† Treated 6 weeks after previous treatment with meecholy.

‡ Joints on right and left side treated on alternate days.

§ Joint was screened with lead, thus preventing any Roentgen rays from penetrating the joint.

¶ Cases also presented in Table 2.

of 20 to 30 milliamperes and was then maintained at that level throughout the treatment. At the end of treatment, the current was slowly reduced.

To 4 patients large doses of histaminase* were given orally throughout 1 day preceding and 2 days during treatment with iontophoresis, using histamine phosphate as the dilating drug. Twenty-four 3-unit capsules were administered daily in three equally divided doses. This was done to determine whether the undesirable systemic effects of histamine (flushing, dizziness, headaches, and fullness in the head) could be inhibited or reduced by this enzyme.

Results. A total of 661 treatments were given; as many as 66 and as few as 5 treatments were given per patient—the average being 23. Fourteen of the 28 patients received 17 or more treatments.

In order to analyze the results, the 28 patients were divided into three groups. In the first group (Table 1) results of iontophoresis treatment of comparably diseased joints using different vasodilating drugs are presented; in the second group (Table 2) the results of iontophoresis therapy to the same joints employing different vasodilating drugs are shown, and in the last group (Table 3) the results of iontophoresis therapy are compared with the results of other physical therapy or the condition of untreated control joints.

Symptomatic response following therapy has been analyzed separate from the objective changes. Results have been classified as marked, moderate or slight improvement, no change, or worse.

If only the subjective effects are considered, the majority of patients treated with iontophoresis were significantly benefited. Of the 28 patients, 22 (79%) reported some degree of symptomatic benefit. Fourteen patients (50%) reported symptomatic improvement of a moderate or marked degree. Six patients were either unimproved or worse.

In sharp contrast to these subjective observations are the findings based on examination of the treated joints. Of the 28 patients, only 3 (11%) were found to be either slightly or moderately improved when critically examined during the follow-up period; in no instance was marked improvement noted, and 25 patients (89%) were either unimproved or worse.

It should be emphasized that the duration of the subjective improvement usually persisted for only 4 to 6 hours after each treatment. In only 3 cases (Nos. 8, 9 and 16) did the symptomatic improvement continue after the completion of the series of treatments. In Case 8, benefit lasted for 2 months, then all symptoms returned to the pretreatment level. In Case 9, all former symptoms returned 3 weeks after the last treatment. In Case 16, improvement continued for 5 months following the completion of the series of treatments, but the untreated comparably diseased joints of the opposite side improved to an equal degree, so that we feel certain that the reported benefit should be attributed to a spontaneous remission of the disease and not to the use of vasodilating drugs administered by iontophoresis.

* Histaminase (Torantil) was supplied through the courtesy of The Winthrop Chemical Company, New York City.

We were unable to detect any difference in the degree of local erythema, sweating or increase in skin temperature produced by mecholyl, histamine phosphate, or histamine dihydrochloride (imadyl). However, wheal formation associated with pruritus was *always* observed when either histamine phosphate or histamine unction was used. The size and number of the patches of urticaria were distinctly less after imadyl than after histamine phos-

TABLE 2.—RESULTS OF IONTOPHORESIS TREATMENT TO THE SAME JOINTS EMPLOYING DIFFERENT VASODILATING DRUGS.

Case No.	Age and sex.	Duration of disease (yrs.).	Activity of disease (grade).	Joints treated.	Drugs used.	No. of treatments. (total).	Period of follow-up (mos.)	Results of therapy.
9	32 F	5	II	Rt. elbow, wrist and foot	Mecholyl Imadyl Mecholyl	22 4 6 32	9	Subj.: sl. red. in swelling and sl. incr. in motion; incr. local heat persisted 3 hrs.; patient pref. mecholyl to imadyl. Obj.: sl. incr. in motion; patient stated benefit lasted 3 wks.
10	60 M	1	III	Rt. wrist and knee	Mecholyl Histamine phosphate Imadyl	7 4 19 30	17	Subj.: mod. relief of pain lasting only 2 wks. after treat. Obj.: equal local effect with each drug.
11	63 M	10	I	Lt. wrist Lt. ankle Lt. knee Lt. ankle Lt. knee Lt. ankle	Mecholyl Imadyl Mecholyl	11 10 4 25	1	Subj.: mod. relief of pain and stiffness with each drug, sl. more with mecholyl. Obj.: sl. red. in tenderness and swelling in treated joints only.
12	62 M	2	II	Both knees	Histamine phosphate Imadyl	7 7 14	6	Subj.: Marked immed. relief of pain. Obj.: none.
13	50 M	6	II	Rt. knee, wrist and hand	Mecholyl Imadyl Mecholyl Histamine phosphate	16 9 15 6 46	4	Subj.: mod. red. of pain with each drug; with imadyl, intense pruritus; histamine phosph. prod. intense generalized flush and pruritus; patient pref. histamine phosphate. Obj.: none.
14	46 F	3	II	Rt. wrist and lt. ankle	Mecholyl Imadyl Histamine phosphate	20 29 2 51	13	Subj.: mecholyl and imadyl gave mod. temp. relief of pain of equal degree; patient unable to disting. bet. them. Obj.: with imadyl a burn was prod.: histamine phosph. prod. intense generalized flush.
15	32 F	5	I	Both knees	Mecholyl Imadyl	13 15 28	12	Subj.: sl. red. in all symp. during treat. which persisted for 3 to 4 hrs. only. Obj.: none.

TABLE 3.—RESULTS OF IONTOPHORESIS TREATMENT COMPARED WITH THE RESULTS OF OTHER PHYSICAL THERAPY OR THE CONDITION OF UNTREATED CONTROL JOINTS.

Case No.	Age and sex.	Duration of disease (yrs.).	Activity of disease (grade).	Joints treated.	Drugs used.	No. of treatments.	Joints treated by other physical therapy or untreated.	Period of follow-up (mos.).	Results of therapy.
10	47 M	4	II	Lt. knee and ankle	Meccholyl	39	Comparably diseased lt. knee and lt. ankle were untreated	5	Subj.: for 4 hrs. after treatments joints were sl. less painful and tender. Obj.: no immed. change; 5 mos. after treatment control untreated and treated joints mod. improv.
17	50 F	4	II	Lt. elbow hand and knee	Imadyl	8	Comparably diseased lt. elbow, hand and knee; total 1200 r per joint	4	Subj.: no change with iontophoresis; sl. less pain after second series of Roentgen ray therapy. Obj.: no change.
18	58 M	4	II	Rt. wrist and knee	Meccholyl	5	Same joints treated for 4 mos. with whirlpool baths	17	Subj.: pain and stiffness sl. worse after each treatment; patient requested treatments discont. Obj.: none. Much preferred whirlpool baths.
19	42 F	21	II	Lt. wrist hand and ankle	Meccholyl	5	Comparably diseased rt. wrist, hand and ankle; 600 r Roentgen irradiation to each joint	20	Subj.: none. Obj.: none.
20	29 F	3	III	Lt. hand and knee	Meccholyl	38	Comparably diseased rt. hand and knee treated by Roentgen irradiation; total, 1800 r to each joint	21	Subj.: all joints treated by iontophoresis were mod. worse; no change after Roentgen irradiation. Obj.: none.
21	60 F	3	II	Lt. ankle and foot	Imadyl	5	Same joints treated later for 1 mo. by hot paraffin applications twice daily	9	Subj.: no change after imadyl; marked relief of symptoms after hot paraffin applications. Obj.: none. No lasting benefit after paraffin.

22	56 M	8	II	Rt. ankle and foot	Mecholyl	9	Comparably diseased lt. elbow, hand, knee and ankle treated by Roentgen rays; total, 1800 r to each joint	11	Subj.: mod. relief of pain during mecholyl treatments; all joints slowly improv. dur- ing observ. period; Roentgen irradiated joints mod. improv. Obj.: mod. improv. in all joints of equal degree.
23	62 F	10	IV	Lt. elbow knee and ankle	Mecholyl	29	Comparably diseased rt. elbow, knee and ankle treated by Roentgen irradiation; total, 1200 r to each joint	1	Subj.: none with either method of therapy. Obj.: none.
24	67 F	12	II	Rt. ankle	Imadyl	11	Comparably diseased lt. ankle treated with 600 r Roentgen ray irradiation	2	Subj.: mod. immed. relief of pain after both types of therapy. Obj.: none. Patient highly susceptible to suggestion and attention.
25	36 M	1	III	Rt. ankle	Imadyl	6	Comparably diseased lt. ankle and wrist treat- ed with 600 r Roent- gen ray	1	Subj.: mod. relief of all sympt. after imadyl; liked treatments very much; 1 mo. later all joints sl. worse than before iontopho- resis. Obj.: during treatment no change; 1 mo. later slightly worse.
26	59 M	1½	II	Lt. knee and ankle	Mecholyl	12	Same joints treated for previous 3 mos. by whirlpool baths	1	Subj.: after iontophoresis sl. less pain. Obj.: none. Patient pref. results following whirlpool baths.
27	38 M	4	II	Rt. wrist and knee	Mecholyl	26	Comparably diseased lt. wrist given 1800 r Roentgen ray therapy	1	Subj.: mod. relief of pain during iontopho- resis treatments; no benefit after Roent- gen irradiation; no lasting effect. Obj.: none.
28	28 M	12	II	Lt. knee and foot	Imadyl	9	Comparably diseased rt. ankle untreated	12	Subj. sl. red. in pain in treated joint only. Obj.: none. Extension of arthritis to other joints.

phate solution. The pruritus which followed histamine in either form was objectionable to most patients. Pruritus did not occur during or after treatment with mecholyl.

In none of the 4 patients (Nos. 2, 4, 13 and 14) to whom large doses of histaminase were given orally preceding and during treatment with histamine solution by iontophoresis, were the local effects of histamine altered. In 3 of these patients, general symptoms attributable to histamine (headache, substernal oppression, erythema and urticaria remote from site of iontophoresis) were not changed by histaminase; in 1 patient there was definite reduction in the severity and duration of these general effects of histamine.

Chronic ulcers were produced over the joint treated (by arcing currents under the positive electrode) in 2 patients (Cases 2 and 14). In each instance the drug used at the time was imadyl.

In 15 patients in whom vasodilatation was produced by iontophoresis, other joints (usually comparably diseased) were treated by another type of physical therapy: 12 by Roentgen irradiation, 2 by whirlpool baths, and 1 by hot paraffin baths. Of the 12 patients treated by both Roentgen irradiation and iontophoresis, 7 reported the same effect after each method. For example, if there was no benefit from iontophoresis there was none from Roentgen therapy; if slight or moderate improvement followed one, the other gave the same degree of improvement. Four patients of the 12 treated by both of these methods reported slight or moderate benefit only after iontophoresis. There was improvement after Roentgen therapy with no benefit after iontophoresis in only 1 case. In the 2 patients in whom some joints were treated with iontophoresis and others with whirlpool baths, both patients preferred the latter. The one patient treated first by iontophoresis and later by hot paraffin baths benefited only from the hot paraffin baths. In this case, however, only 5 iontophoresis treatments were given.

Discussion. Appraisal of any new form of treatment, whether general or local, for rheumatoid arthritis is a most difficult problem and requires careful consideration of many factors. Spontaneous remissions are frequent and one should always be keen to recognize them whenever possible. For instance, in Case 16 only one of each pair of comparably diseased joints was treated by iontophoresis; the other was left untreated and thus served as a control. Study 5 months after the series of treatments revealed that both treated and untreated joints were equally improved. Without such a controlled study, the improvement which occurred undoubtedly, during spontaneous remission, might have been erroneously attributed to iontophoresis therapy.

In estimating the true value of a therapeutic agent in patients with rheumatoid arthritis, the psychologic effect must also be considered. No other group of patients responds more favorably to attention, care, encouragement, and suggestion than do individuals afflicted with chronic arthritis. One could hardly devise a more

effective means of obtaining the maximum psychic stimulation than is offered by iontophoresis. The patient is immediately impressed by the elaborate technical procedure and the highly detailed attention of the trained operator. The galvanic machine buzzes and the skin is stimulated by the electric current. All of these factors may be, and frequently are, strong psychic stimuli and we feel that they have not been sufficiently considered by many others who reported so favorably concerning this method of therapy.

If we judge solely on the basis of the *symptomatic* improvement *during the period of treatment* our results are encouraging. However, the lack of objective improvement and the practically universal recurrence of all symptoms to the pretreatment level soon after the completion of treatment, clearly indicates that iontophoresis afforded no lasting benefit to our patients.

In the majority of cases where the results from vasodilating drugs administered by iontophoresis could be compared with the results following other local measures of physical therapy, no advantage with the former method of treatment was observed. We have found iontophoresis to be a reliable way of producing localized temporary increase in circulation, but it appears to have no important advantage over the less expensive and more accessible commonly employed methods of physical therapy. It has the disadvantages of being time-consuming, requiring a trained technician and special equipment. Chronic skin ulcers occasionally occur under electrodes. Further, in this chronic disease, physical therapy must be continued for long periods of time and the cost of iontophoresis seems prohibitive except for wealthy patients.

Summary. Twenty-eight patients with rheumatoid arthritis have been treated under carefully controlled conditions using different vasodilating drugs administered by iontophoresis. Of the patients treated, 79% were partially relieved of their joint symptoms during and for a short time after the treatment. However, few patients had significant *objective* evidence of improvement attributable to iontophoresis. It serves as another reliable means of physical therapy but offers no important advantages over other commonly employed methods. It has distinct disadvantages: it requires special equipment and a trained operator; and it is expensive. On the basis of our carefully controlled study, we believe that the disadvantages attending this form of treatment, in comparison with the few real advantages, preclude its widespread employment.

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BOOK REVIEWS AND NOTICES

FROM CRETIN TO GENIUS. By DR. SERGE VORONOFF. Pp. 281. New York: Alliance Book Corporation, 1941. Price, \$2.75.

This book by the widely known—many would say notorious—advocate of rejuvenation and gland grafting—from the scientific point of view suffers from so many basic disadvantages that it seems bound to do more harm than good. Unlikely and unwarrantable working hypotheses are presented, such as that spirit is matter itself, that thought is the projection of grains of thinking matter, that genius proceeds by inspiration from certain groups of cells distinct from those used for habitual thinking (p. 12), and that these may survive even in the cretin. This, by the way, is about the only appearance of the word cretin that the Reviewer finds. "Can matter think" is posed as a problem, either the soul being accepted as entirely distinct from mind; or mind, as an immaterial essence, not being a product of the cerebrum. To be sure, some entertaining examples of the precocity and struggles of genius, and of the creative process in action are given. For those scientifically minded, however, the book is a waste of time; others who are in danger of being misled by its non-constructive, dubious reasoning, should at least be vary of its unwelcome recklessness of enterprise.

E. K.

PNEUMOCONIOSIS (SILICOSIS). The Story of Dusty Lungs. A Preliminary Report. By LEWIS GREGORY COLE, M.D., Director of Silicotic Research, John B. Pierce Foundation, New York City, and WILLIAM GREGORY COLE, M.D., New York City. Pp. 21; illustrated. New York: John B. Pierce Foundation, 1940.

THIS monograph presents a summary of the authors' views on silicosis as previously published in *Radiology* (33, 261, 1939) and the *Journal of the American Medical Association* (113, 1216, 1939). Reprints of these two articles are included in the book. The authors distinguish four types of silicosis: 1, the diffuse perivascular-peribronchial-lymph node type of Pancoast; 2, the generally accepted nodular type; 3, a pockmarking type; and 4, acute silicosis. There is a discussion of the pathologic anatomy and roentgenology of these four types as well as of the social, economic and legislative problems involved. There are no illustrations, but reference is made to numerous Kodachrome photomicrograph, roentgenograms and microscopic sections which were available "to all serious investigators of pathology" at the offices of the John B. Pierce Foundation, New York City. As to the question of compensation, the authors believe that Pancoast's type was harmless and should not be "compensable"; the nodular type, which in the past was the only one recognized by the law, should be compensatable only if there were dyspnea or other clinical signs, or if it was complicated by tuberculosis; while the pockmarking and acute types, which hitherto were unrecognized and not accepted as silicosis, are said to by all means to be compensatable. Though the monograph lacks completeness (little attention is paid to the literature, there is no discussion of the chemical aspects, and a consideration of tuberculosis is left for a later publication), nevertheless the Reviewer looks upon it as an interesting addition to the literature on silicosis.

W. E.

HIPPOCRATIC MEDICINE. Its Spirit and Method. By WILLIAM ARTHUR HEIDEL. Pp. 149. New York: Columbia University Press, 1941. Price, \$2.00.

From this little book one may get a better comprehension of the background and essence of Hippocratic medicine than from many a larger treatise. Prepared at the invitation of the Macy Foundation as a preliminary to a larger work on Greek science, this volume was fortunately completed just before the author's untimely death. Following a brief sketch of the remarkable beginnings of Greek science in the sixth and fifth centuries B.C., the author considers the science and the medicine of the Hippocratic period, choosing as an appropriate characterization of the Hippocratic literature, the casual remark in Epidemics I that there are three factors concerned in every case: the disease, the patient and the doctor. When one reflects that the Greeks did not practice either dissection or the experimental method and had no numeral system conducive to quantitation, one must agree with the author as to the singular insight of the Hippocratics into medicine. It was best exhibited in their powers of observation and prognosis and their principles of treatment, which they modestly limited to preserving health or gently aiding the *vis medicatrix naturæ*.
E. K.

XANTHOMA AND OTHER DYSLIPOIDOSES. By FRED D. WEIDMAN, M.D., L. NAPOLEON BOSTON, M.D., JOSEPH STOKES, JR., M.D., Howard W. SCHAFER, M.D., WALTER FREEMAN, M.D., and F. W. SUNDERMAN, M.D., Philadelphia. Pp. 195; illustrated. Philadelphia: University of Pennsylvania Press for the Authors, 1941. Price, \$3.00.

THIS volume is composed of papers on xanthoma and related disorders published during the past 17 years by Weidman and various associates. These studies have been integrated by an added short chapter on pathology, and by an index. The disconnectedness which might be expected in a volume of reprints is not apparent. Each paper in the present volume fits well into the composite which Weidman must have envisaged throughout his experimental and clinical observations. The senior author is well known as an outstanding dermatopathologist, and the book is especially informative concerning the histopathology of xanthoma. The general medical implications of the lipoidoses are well covered, with the possible exception of their relation to cardiovascular changes. No one can read this volume and still regard xanthoma as primarily a disease of the skin. In common with other authorities, Weidman objects to the term "xanthoma," as it is not a neoplasm, and prefers "xanthosis." Familiarity with these studies will be of value to the internist, and is an essential for the practitioner or student of dermatology. It is hoped that the reception of this volume will stimulate the author to further collections of studies of skin histopathology and continued emphasis on their importance in the interpretation of the general medical state of the patient.
D. P.

THE FURTHERANCE OF MEDICAL RESEARCH. By ALAN GREGG, M.D., Director for the Medical Sciences at the Rockefeller Foundation. Pp. 129. New Haven: Yale University Press, 1941. Price, \$2.00.

It is a trite but none the less true observation that private foundations for the prosecution and aid of scientific investigation these days are working in difficult times with a prospect of more difficulties still to come. Investment returns have dwindled, costs have risen, government activities have widened, and unexpected emergencies have produced new urgent needs that necessarily hinder a progress that has been in some ways phenomenal

in this country in the near past. None knows these difficulties better than the heads of the great charitable foundations that have done so much to help the chronically indigent educational schools and universities.

It is therefore peculiarly appropriate that the Director for the Medical Sciences at the Rockefeller Foundation should at this time discuss in this 18th series of Terry Lectures how universities and foundations should best plan to meet their responsibilities in furthering medical research. In the first lecture, the author defines medical research and considers its setting in modern society, its essential components, and some of its resources, achievements and handicaps. In the second he considers what the universities and foundations have done and should do in the matter, calling attention to some of the pitfalls and the defective relationships between universities and foundations. Practical suggestions are offered for the organization of a foundation, its approach to the formation of a general policy, the study of projects requesting aid, its reports and a *verb. sap.* as to what a foundation's experience will probably be. In the last lecture, the medical research workers, "the most important and yet the most misunderstood factors in the furtherance of medical research" are considered. As one who constantly sets his face toward the unknown, the investigator must observe well—"be alert to revelations that nature may give him as she babbles"—or devise problems (*i. e.*, questions "so posed as to have an answer yes or no"), be skillful in analyzing results, ingenious in overcoming obstacles, and shrewd in inferring underlying significances.

These random examples should be sufficient to indicate the wealth of interest that this small book contains for research workers and university and foundation administrators. E. K.

THE MAN WHO LIVED FOR TOMORROW. A Biography of William Hallock Park, M.D. By WADE W. OLIVER. Pp. 507; 1 illustration. New York: E. P. Dutton & Co., Inc., 1941. Price, \$3.75.

THIS is a sympathetic story of the life of a tireless worker, who when receiving an honorary degree was described by "Billy" Phelps as "the perfect type of scientist in the service of the State." His major achievements were so long and so closely connected with the New York City Department of Health that the new William Hallock Park Laboratory was fittingly dedicated to him in the closing years of his life. Though his modest statement, "I have done nothing alone," should not be taken too literally, he does stand out prominently—at a time when preventive medicine was achieving major progress in this country—as the administrator-investigator whose wise selection of assistants and support of timely problems advanced public health far more than would have been accomplished by his unaided efforts. The control of poliomyelitis, milk contamination, pneumonia, scarlet fever and numerous other contagious diseases was significantly furthered by him, in addition to his best-known achievement, the perfection of diphtheria immunization. Those who wish to delve further into such matters will find much satisfaction in this well-written study by a friend who is himself an excellent scientist. E. K.

THE MEDICAL CLINICS OF NORTH AMERICA, Vol. 25, No. 6, November, 1941. Military Medicine. Pp. 417; 49 illustrations. Philadelphia: W. B. Saunders Company, 1941.

FOLLOWING a graceful Foreword by Rear Admiral McIntire, Surgeon-General of the Navy, there are 18 excellent presentations forming a Symposium on Military Medicine. The first concerns the part played by the

physician in Selective Service; the second Medical Organization in the Permanent Camp and in the Field. The remaining 16 cover a special phase of medicine—each written by an expert and presented with an eye to practical military conditions. This is not an easy task, for it requires an intimate knowledge of both medical and military conditions. A guarantee of the success of this undertaking is found in the names of the authors; all but 3 of the 26 being officers in the Army or Navy. The Reviewer cannot list all of the authors or their topics, but he cannot resist mentioning Major-General Reynolds on Tuberculosis, Colonel Howe on Nutrition, and Major de Lormier on X-ray Examination of the Chest, whose contributions seem to rise even above the high level of the other articles.

This symposium will prove of great value not only to medical officers but to physicians in civil practice. It could well be read by many others for the purpose of gaining an insight into the extent of military medical problems and the measures being taken to meet them. O. P.

DISEASES OF THE NERVOUS SYSTEM Described for Practitioners and Students. By F. M. R. WALSH, O.B.E., M.D., D.Sc., F.R.C.P. (LOND.), HON. D.Sc. (NAT. UNIV. IRELAND), Physician-in-Charge of the Neurological Department, University College Hospital, London; Physician to the National Hospital for Nervous Diseases, Queen Square; Neurologist to the National Hospital for Tropical Diseases, London, and the Seamen's Hospital, Greenwich. Pp. 325; 32 illustrations. Second edition. Baltimore: The Williams & Wilkins Company, 1941. Price, \$4.50.

In this small book the effort has been to select only such neurologic matter as shall best meet the needs of the medical student and general practitioner. Many extravagant terms employed by some professional neurologists have been avoided. Since it is denied that there is any practicable method of grouping nervous diseases, no such plan is attempted. The subject-matter is presented in two sections: a general statement of the principles of neurological diagnosis, with brief characteristic descriptions of symptom-complexes; and accounts of the commoner nervous diseases. Additions have been made to the sensory, visual and speech functions; also to intracranial tumors and pituitary diseases; with new chapters on acute infections, head and spinal injuries, and lesions of the spinal nerves. The presentation shows a dogmatic tendency which may lead to overconfidence with the inexperienced. [It is difficult to see how this and other obvious weaknesses can be avoided when such a large subject is presented in such small space.—EP.] N. Y.

INFANT NUTRITION. A Textbook of Infant Feeding for Students and Practitioners of Medicine. By WILLIAM MCKIM MARRIOTT, B.S., M.D., Late Professor of Pediatrics, Washington University School of Medicine; Physician-in-Chief, St. Louis Children's Hospital. Revised by P. C. JEANS, A.B., M.D., Professor of Pediatrics, College of Medicine, State University of Iowa, Iowa City. Pp. 475; 31 illustrations. Third Edition. St. Louis: The C. V. Mosby Company, 1941. Price, \$5.50.

THIS well-known and classic text by the late Dr. Marriott has been brought completely up to date by Professor Jeans of the University of Iowa, who brings to the task a rich experience and a stimulating youthful point of view. The book's purpose is "to summarize present-day knowledge concerning the nutritional requirements under normal and pathologic conditions and to indicate the effects of failure to meet any or all of these requirements."

In concise but comprehensive fashion its 32 chapters discuss the fundamentals of growth, metabolism, food requirements, digestion, breast and artificial feeding, diets, and the common nutritional disorders, an understanding of which matters is essential to all pediatricists or practitioners who assume the responsibility for medical supervision of babies during their first year of life. The book's style is simple and direct, the approach clinical, conservative and practical, and the mass of contained material enormous but thoughtfully interpreted. Recent advances in such fields of contemporary activity as intracellular metabolism and food technology, when pertinent, are referred to, and some of Kornfeld's data on height and weight in relation to age have been included in the form of very practical charts. One notes with interest the advice to begin the feeding of puréed fruits and vegetables before the introduction of cereals because of the higher content of thiamine and iron in the quantities usually recommended for infant feeding.

The editors or authors have chosen to omit a bibliography, so that the student unfortunately receives no help in referring to original sources for critical analyses or more exhaustive reading.

I. W.

THE AVITAMINOSES. The Chemical, Clinical and Pathological Aspects of the Vitamin Deficiency Diseases. By WALTER H. EDDY, PH.D., Professor of Physiological Chemistry, Teachers College, Columbia University, etc., and GILBERT DALLDORF, M.D., Pathologist to the Grasslands and Northern Westchester Hospitals, Westchester County, N. Y. Pp. 519; 28 illustrations and 40 plates. Second Edition. Baltimore: The Williams & Wilkins Company, 1941. Price, \$4.50.

In its second edition this book has been largely rewritten, and much new material has been added. A new chapter on Vitamins and Cellular Oxidation has been inserted to meet the needs of readers whose academic chemistry did not include present-day concepts of biologic oxidations, in which many of the vitamins have been shown to play a rôle.

Two chapters are devoted to each vitamin, the first to discuss its nature and function, the second for a thorough review of the specific deficiency syndrome, the latter including full discussion of the clinical aspects, morphologic changes and pathologic physiology. A bibliography is added to each chapter.

Laboratory tests useful in diagnosis and treatment and tables of the vitamin content of foods are given. Unfortunately, the figures for vitamin values of foods are so presented that, except in the case of nicotinic acid, it is impossible to do more than determine the relative vitamin content of foods. In the light of the general excellence of the book, however, this omission, which a future edition can readily correct, is very slight.

The illustrations are numerous and clear.

E. W.

FUNCTIONAL PATHOLOGY. By LEOPOLD LICHTWITZ, M.D., Chief of the Medical Division of the Montefiore Hospital; Clinical Professor of Medicine, Columbia University. Pp. 567; 157 illustrations. New York: Grune & Stratton, Inc., 1941. Price, \$8.75.

Good books on functional pathology in English are more needed than are those stressing the structural aspects of the subject; however, we are now strengthened in our opinion that they should be written by qualified pathologists rather than by clinicians. If, as the advertisement of this book states, "a truly medical viewpoint dominates," and discussion is "always from a diagnostic and therapeutic standpoint," then the book would be more accurately described by a different name.

Though the author has "not attempted to cover the entire field," the 28 chapters include a wide range—Endocrinology, Metabolism, Defense Mechanisms, Hypertension, Blood Diseases, Bright's Disease, Hepatic Disorders. Topics are presented without much regard for logical sequence: the endocrines, for instance, are considered at some length in five different parts of the book. As the book is "deliberately written from a very personal viewpoint," one need not be surprised at the dogmatic style, the preponderance of Teutonic references and points of view, and the occasional neglect of some important Anglo-Saxon contributions. The book should be approached more as a thought stimulator than as a well balanced, authoritative statement—but perhaps this was the author's intention.

Illustrations are few but adequate. The unpleasant odor of the coated paper will presumably soon disappear. The price seems unnecessarily high. E. K.

X-RAY THERAPY OF CHRONIC ARTHRITIS (Including the X-ray Diagnosis of the Disease). Preliminary Report Based on 100 Patients Treated at Quincy, Illinois. By KARL GOLDHAMER, M.C., Associate Roentgenologist, St. Mary's Hospital and Quincy X-ray and Radium Laboratories, etc. With a Foreword by HAROLD SWANBERG, B.S., M.D., F.A.C.P., Roentgenologist, St. Mary's and Blessing Hospitals. Pp. 131; 24 original illustrations by author, 2 roentgenograms and 4 tables. Quincy, Illinois: Radiologic Review Publishing Company, 1941. Price, \$2.00.

THIS monograph is replete with practical information concerning atrophic and hypertrophic arthritis. The author makes no attempt to discuss other forms of joint disease except when necessary in discussing the differential diagnosis. The first portion of the book outlines the pathologic and clinical aspects of chronic arthritis, little attention being given to the therapeutic aspects. The Roentgen findings are discussed in detail. Pencil sketches instead of roentgenograms are used as illustrations, but the effect is satisfactory as the drawings are unusually fine. Included in these illustrations are the characteristic findings of atrophic arthritis of joints, hypertrophic arthritis of joints, atrophic spondylitis and hypertrophic spondylitis. The remaining portions are concerned with Roentgen therapy. The author attempts to explain why irradiation is beneficial in chronic arthritis, and some facts and theories concerning the use of Roentgen rays in infections are reviewed.

Of 100 patients with chronic arthritis, approximately 28% were clinically cured, marked improvement was obtained in 31%, slight improvement in 29%. There were 12% failures. The general effects of irradiation were the relief of pain, tenderness and increased freedom of motion.

The Roentgen technique is outlined in detail. The treatment method is practical and clearly defined. P. H.

THE MEDICAL CLINICS OF NORTH AMERICA, VOLUME 26, No. 1 (Chicago Number, January, 1942). Pp. 313; 45 illustrations. Philadelphia: W. B. Saunders Company, 1942.

THIS issue introduces a new format: The binding has attractive stamping; the type is more easily read. Side headings set off in black-face type, make it convenient to pick out the part of any discussion one wishes to consult.

This number deals mostly with a symposium on the treatment of common skin diseases by a group of eminent dermatologists from Chicago. The range of subjects covers nearly all the essentials, for the practitioner. For the most part, generally accepted modern viewpoints are expressed; but

we are hardly in accord with the recommended concurrent use of arsenicals and bismuth compound for treatment of early syphilis. Probably because of limitation of space, certain subjects receive less attention than they deserve. As a whole, however, the presentations offer the practitioner a rapid authoritative review of practical dermatology. The volume also contains practical papers on various other aspects of medicine.

H. B.

A HANDBOOK OF OCULAR THERAPEUTICS. By SANFORD R. GIFFORD, M.A., M.D., F.A.C.S., Professor of Ophthalmology, Northwestern University Medical School, Chicago; Attending Ophthalmologist, Passavant Hospital, Wesley Memorial Hospital, Cook County Hospital. Pp. 410; 69 illustrations. Philadelphia: Lea & Febiger, 1942. Price, \$4.00.

THE popularity of this excellent textbook is attested to by the fact that it has already gone through three editions since 1937. There is perhaps no one better qualified than the author to write a book of practical treatment for the graduate student and practicing ophthalmologist. The illustrations are excellent. There is a useful bibliography at the end of each section.

F. A.

BEHIND THE MASK OF MEDICINE. By MILES ATKINSON. Pp. 348. New York: Charles Scribner's Sons, 1941. Price, \$3.00.

"WHY, he let my father die without telling him his heart trouble was serious." "Why can't they mercifully put mother to sleep, the way the veterinarian did with our dog?" "Why does he send me around to a lot of expensive consultants instead of giving me some medicine?" "Why won't Dr. Blank take me on as his patient just because he had been called in earlier as a consultant?" Covered by the mask of medicine, these are some of the questions which should make the medical man want his patients to read this wise and instructive book.

The author, now for 6 years a New York City practitioner, was a successful general surgeon, then otolaryngologist, in England. A member of the B. E. F. in 1914, a graduate of Barts, a surgeon in the Royal Navy in the last war, he rose to distinction at home (Jacksonian Prize winner and Hunterian Professor of Surgery in the Royal College of Surgeons). He combines to an unusual degree professional knowledge with a broad, sane view of the complexities of medicine's relation to the public. Following 2 brief but well-selected historical chapters on the peaks of medical progress, various medical customs are considered which are generally misunderstood by the laity. The proper use to be made of specialists and many consultations in obscure cases, the continuing central position of the family doctor, the objections to euthanasia, the logical basis for "profession etiquette" from the patient's as well as the physician's point of view, the far-reaching changes in medical economics produced by medical progress, why the doctor's bill is the last to be paid, the incubus of the oversized hospital, the socializing of medical practice—these are all problems of practical importance in the physician-patient relationship that are elucidated in this valuable book.

E. K.

SOURCE BOOK OF MEDICAL HISTORY. Compiled with Notes by LOGAN CLENDENING, M.D., Professor of the History of Medicine, University of Kansas. Pp. 685. New York: Paul B. Hoeber, Inc., 1942. Price, \$10.00.

ANYONE who has ever browsed with any regularity through this department of our journal cannot help but have noticed the increasing number of

"anthologies" recorded, and the favorable comment that they have aroused. The urge to go back to original descriptions—or to translations, as must unfortunately be the case in these uncultured days—has thus been considerably stimulated, to the reader's profit and often to the advantage of medical publishing in saving the space of needless repetition.

This latest compilation of the anthology type has the added recommendation of having been prepared by one of the most experienced and distinguished medical historians in this country, who is also a writer of unusual discrimination and expressiveness. Dr. Clendening gives us the most complete of any of these anthologies and has used an approach different from the usual one. Following a chronologic sequence, from the Egyptians to the 20th century, he presents excerpts from 148 of the most significant contributions to the progress of medicine in all its branches, including some selections from the lay literature of the period under consideration. One too seldom finds elsewhere that the portals of medical literature were passed by Aristophanes, the Arabian Nights, Chaucer, Molière, Le Sage, Thackeray, Dickens, and John Brown's Rab. We not only read the actual words of Sydenham, let us say, in what Clendening has selected as his four most important contributions, but we also find concise introductory remarks on each subject with references for more extended reading. One misses selections from the 20th century—perhaps the most important on an annual basis of any century in the history of medicine. If limitations of space dictated their exclusion, a suggestion toward gilding the lily would be to give the reader a further profit from Dr. Clendening's special knowledge by the addition in the next edition of an addendum of a short-title list of the most significant contributions in this century.

E. K.

SKIN GRAFTING from a Personal and Experimental Viewpoint. By EARL CALVIN PADGETT, M.D., F.A.C.S., Professor of Clinical Surgery, University of Kansas School of Medicine, Kansas City. Pp. 149; 65 illustrations. Springfield, Ill.: Charles C Thomas, 1942. Price, \$4.50.

For the last few years the name of Padgett has been associated in the minds of surgeons with skin grafting because of his ingenious and useful instrument, the Dermatone. It is not surprising that a surgeon interested enough in the problem of skin grafting to conceive such a device would have a wide experience in this field and be able to discuss critically the contributions of others.

This excellent little book has only the defect of being too brief. One wishes that Doctor Padgett would include in his next edition more details of his technique, in addition to showing the final results, for then this might be more useful as a manual to surgeons. The volume, even as it is, will be very useful at a time when skin grafting may be an important problem in our armed forces and in the civilian population.

I. R.

CLINICAL ROENTGENOLOGY OF PREGNANCY. By WILLIAM SNOW, M.D., Director of Radiology, Bronx Hospital; Roentgenologist-in-Charge, Harlem Hospital, New York City. Pp. 178; 119 illustrations. Springfield, Ill.: Charles C Thomas, 1942. Price, \$4.50.

This is a useful manual containing a summary of present-day radiologic practice in pregnancy, based on the author's extensive experience at two busy hospitals maintained by the City of New York. Illustrations are plentiful and of good quality considering the technical difficulties involved in examinations of patients in late stages of pregnancy. Perhaps the chief virtue of the book is the fact that it brings under one cover the author's

various important contributions toward the interpretation of soft tissue shadows in pregnancy, particularly in regard to pathology of the placenta.

Another attractive feature, found in the last 60 pages, are carefully annotated case reports with roentgenograms. This allows the reader to trace the author's complete analysis of each case, step by step, even to verification of the various pelvic measurements.

Although written as a working guide, there are a few sections of the book where the presentation of material seems unnecessarily confusing. This is true in the first and third chapters which deal with pelvimetry and cephalometry. Here the author is not sufficiently critical in his survey of the various methods employed, and too detailed in the presentation of his own.

One other criticism seems justified and that is the assumption, tacitly made, that the roentgen examination often determines whether Cesarean section is necessary. The author with his wide experience may be correct in many cases where he advises section. Nevertheless, it is highly fallacious and even dangerous for men new in this field to attempt to draw any such sweeping conclusions from the roentgen examination; inasmuch as absolute bony dystocia as shown in the roentgenogram occurs in about 1 in 250 patients with borderline pelves by physical examination.

R. B.

NEW BOOKS.

Nasal Sinuses. An Anatomic and Clinical Consideration. By O. E. VAN ALYEA, M.D., Assistant Professor, Department of Laryngology, Rhinology, and Otology, University of Illinois College of Medicine, Chicago. Pp. 262; 82 illustrations. Baltimore: The Williams & Wilkins Company, 1942. Price, \$6.50.

Diabetes Mellitus. By ZOLTON T. WIRTSCHAFTER, M.D., Clinician in Charge, Clinic for Diabetes, Department of Medicine, Mount Sinai, Cleveland; Visiting Physician, Department of Medicine, Cleveland City Hospital, etc., and MORTON KORENBERG, M.D., Medical Resident, Jewish General Hospital, Montreal. Pp. 186; illustrated. Baltimore: The Williams & Wilkins Company, 1942. Price, \$2.50.

Psychiatry in Medical Education. By FRANKLIN G. EBAUGH, M.D., Professor of Psychiatry, University of Colorado School of Medicine; Director, Colorado Psychopathic Hospital and Division of Psychiatric Education, National Committee for Mental Hygiene, and CHARLES A. RYMER, M.D., Associate Professor of Psychiatry, University of Colorado School of Medicine; Assistant Director, Colorado Psychopathic Hospital. Pp. 619; illustrated. New York: The Commonwealth Fund, 1942. Price, \$3.50.

Anoxia. Its Effect on the Body. By EDWARD J. VAN LIERE, Ph.D., M.D. Pp. 269; 17 illustrations. Chicago: The University of Chicago Press, 1942. Price, \$3.00.

Diseases of Metabolism. Detailed Methods of Diagnosis and Treatment. A Text for the Practitioner. Edited by GARFIELD G. DUNCAN, M.D., Chief of Medical Service "B", Pennsylvania Hospital; Associate Professor of Medicine, Jefferson Medical College, Philadelphia. Fifteen Contributors. Pp. 985; 158 illustrations including 7 plates in color. Philadelphia: W. B. Saunders Company, 1942. Price, \$12.00.

Skin Grafting from a Personal and Experimental Viewpoint. By EARL CALVIN PADGETT, M.D., F.A.C.S., Professor of Clinical Surgery, University of Kansas School of Medicine, Kansas City, Kansas. Pp. 149; 65 illustrations. Springfield, Ill.: Charles C Thomas, 1942. Price, \$4.50.

Roentgen Treatment of Infections. By JAMES F. KELLY, M.D., F.A.C.R., Professor and Director of the Department of Radiology, Creighton University School of Medicine; Attending Radiologist, Creighton Memorial, St. Joseph's, St. Catharine's and Douglas County Hospitals, Omaha, and Mercy Hospital, Council Bluffs. With the Collaboration of D. ARNOLD DOWELL, M.D., Assistant Professor of Radiology, Creighton University School of Medicine, etc. Pp. 432; 122 illustrations. Chicago: The Year Book Publishers, Inc., 1942. Price, \$6.00.

Methods of Treatment in Postencephalitic Parkinsonism. By HENRY D. VON WITZLEBEN, Elgin State Hospital, Elgin, Illinois. Preface by THEODORE J. C. VON STORCH, Associate Professor of Neurology, Albany Medical College; Attending Neurologist, Albany Hospital. Pp. 164. New York: Grune & Stratton, 1942. Price, \$2.75.

Modern Bread from the Viewpoint of Nutrition. By HENRY C. SHERMAN and CONSTANCE S. PEARSON, Columbia University. Pp. 118. New York: The Macmillan Company, 1942. Price, \$1.75.

The Eclipse of a Mind. By ALONZO GRAVES. Pp. 722. New York: The Medical Journal Press, 1942. Price not given.

Conceptional Thinking in Schizophrenia. (Nervous and Mental Disease Monographs, No. 67.) By EUGENIA HANFMANN, Ph.D., Instructor of Psychology, Mount Holyoke College, and JACOB KASANIN, M.D., Chief, Psychiatric Service, Mount Zion Hospital, San Francisco; Assistant Clinical Professor of Psychiatry, University of California Medical School. Pp. 115. New York: Nervous and Mental Disease Monographs, 1942. Price, \$2.50.

The Diseases of the Basal Ganglia. (Proceedings of the Association December 20 and 21, 1940, New York.) (Vol. XXI of Research Publications Association for Research in Nervous and Mental Disease.) Pp. 719; 268 illustrations. Baltimore: The Williams & Wilkins Company, 1942. Price, \$10.00.

The Treatment of Burns. By HENRY N. HARKINS, M.S., M.D., Ph.D., F.A.C.S., Associate Surgeon, Henry Ford Hospital, Detroit; Formerly Instructor in Surgery, University of Chicago, etc. Pp. 457; 120 illustrations, 16 charts and 40 tables. Springfield, Ill.: Charles C Thomas, 1942. Price, \$6.50.

From Infancy Through Childhood. By LOUIS W. SAUER, M.D., Ph.D., Assistant Professor of Pediatrics, Northwestern University Medical School, Chicago; Physician, Evanston Hospital, Evanston, etc. Pp. 200; 13 illustrations. New York: Harper & Bros., 1942. Price, \$2.00.

Industrial Surgery. Principles, Problems and Practice. By WILLIS W. LASHER, M.D., F.A.C.S., Assistant Professor of Traumatic Surgery, New York Post-Graduate Medical School, Columbia University; Assistant Attending Surgeon, New York Post-Graduate Hospital, etc. With a Foreword by CHARLES GORDON HEYD, M.D., Past President, American Medical Association. Pp. 472; 193 illustrations. Enlarged First Edition. New York: Paul B. Hoeber, Inc., 1942. Price, \$6.50.

NEW EDITIONS.

Textbook of Embryology. By HARVEY ERNEST JORDAN, M.A., Ph.D., Sc.D., Professor of Anatomy and Director of the Anatomical Laboratories, University of Virginia, and JAMES ERNEST KINDRED, M.A., Ph.D., Professor of Anatomy, University of Virginia. Pp. 613; 470 illustrations and 31 plates. Fourth Edition. New York: D. Appleton-Century Company, Inc., 1942. Price, \$6.75.

PROGRESS OF MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY.

UNDER THE CHARGE OF

JOSEPH C. BECK, M.D.,

ASSOCIATE PROFESSOR EMERITUS, DEPARTMENT OF OTO-LARYNGOLOGY, UNIVERSITY
OF ILLINOIS COLLEGE OF MEDICINE,

AND

NOAH D. FABRICANT, M.D.,

ASSOCIATE, DEPARTMENT OF OTO-LARYNGOLOGY, UNIVERSITY OF ILLINOIS
COLLEGE OF MEDICINE,
CHICAGO, ILLINOIS.

THE PRESENT RÔLE OF VITAMINS IN OTOLARYNGOLOGY.

At first glance it may seem hardly necessary in a current review of the present rôle of vitamins in otolaryngology to preface a specific discussion with a general statement on vitamins. However, it is because the literature is filled with pros and cons—indeed, in some quarters the verbal shot-and-shell is dipped in vitriol—that, with apologies, we quote Camp³ at length. "Little did Casimir Funk realize," writes Camp, "when he coined the word 'Vitamine' that he was furnishing the catchword for a \$100,000,000 business. Probably nothing medical has captured the imagination of the public so thoroughly as the vitamin deficiency question. Only in part is this due to advertising; a good share of the fault rests with the medical profession which has indiscriminately prescribed vitamin capsules, tablets, elixirs, etc., on the theory that some good might be obtained, that no harm can result, and that since all is not known about vitamins, there may be some hidden elixir of health, some spark of prolonged life, some all-powerful corrective enclosed in the gelatin seal or compressed tablet. In comparison, one should not smile at the theriacs and treacles of antiquity until one has thoroughly enjoyed the potpourri of the modern vitamin capsule."

"Ironically, the greatest trade in vitamins is in communities where there is sufficient money to provide adequate diet. A person unable financially to provide a balanced diet cannot afford to buy the expensive vitamin products. The self-conviction that one is vitamin-deficient is almost of paranoid quality; the premise is false, but the results are satisfying. Vitamins are a necessity. No one can doubt that living organisms require these substances, but their use should be, and in

these times must be, limited to those individuals who actually require them. A priority on vitamins would do much to settle the embarrassing problem of inadequate supply when there is sufficient for all who need them. There are three classes of people who actually require vitamin therapy: those who have insufficient intake; those who do not absorb them; and those in whom the agent is apparently ineffective when absorbed in ordinary amounts."

"Insufficient intake may be one of two types. A diet by necessity may be so restricted and limited, either due to poverty or disease, that it is unbalanced. In this sense there may also be deficiency in fats, carbohydrates, proteins or minerals. Secondly, an individual who is comparatively healthy and financially able may develop an inadequate diet through individual dislikes to foods, the variety of foods becoming more and more restricted until insufficient vitamins are ingested. This condition is most efficiently and economically corrected by the eating of balanced diets. Naturally, patients on necessarily limited diets must have vitamins added. The eradication of poverty is progressing at a rate consistent with our way of life, and the dietary needs of vitamins is being considered seriously (fortified bread). There is a group of individuals, apparently normal in all respects, who do not have the ability to absorb vitamins when taken in ordinary amounts. If more vitamins are taken, according to the law of mass action, more vitamins are absorbed, and in this way a deficiency may be prevented. A subgroup, large in proportions, is composed of those individuals who prevent absorption by taking cathartics. The more active cathartics eliminate the vitamins, and the oily types (*e. g.*, liquid petrolatum) are apt to dissolve the fat-soluble vitamins (A, D, K, F) and thus prevent their absorption. In the last group are those individuals who, in reality, are not suffering from a lack of vitamins, but rather a disturbance in their internal metabolism. In these the possibility of mass action from additional intake may help to correct the deficiency."

"The statement is too often made that vitamins are harmless. We know that in large amounts they are toxic; however, it is quite difficult to say just what amount may be toxic. Certainly idiosyncrasies exist; therefore, one would think that a toxic action is not beyond plausibility. The possibility exists that the persistent absorption of large quantities of vitamins may so alter cellular metabolism that a higher concentration of vitamins may become a necessity in order to effect a normal intake. The fact that such small quantities are necessary leads one to conclude that these substances are highly active and should not be treated as indifferent harmless substances. They should be used only when actually needed, and not allowed to become a passing fancy (or placebo) for the majority of the people."

In a lengthy review of the relationship of vitamins to ear, nose and throat, Jones⁸ summarizes the knowledge available for use in clinical practice. He believes that it is very simple to deduce a deficiency in either vitamin A or vitamin C when the patient clearly shows evidence of either xerophthalmia or scurvy. The major difficulty involves those patients who have only a moderate deficiency or a mild deficiency, for here it is often exceedingly difficult to make a diagnosis of a lack of one or more vitamins. Of course, the entire matter could be greatly simpli-

fied by the discovery of simple, accurate methods for the determination of moderate or mild vitamin deficiencies. Though certain laboratories are now available, but few clinical laboratories throughout the country are equipped to make the present tests. Thus far, it would appear, the most functional method for physicians to employ is a careful inquiry into the diet of the patient. Jones believes that each vitamin has a preponderant effect on the special structures derived from the ectoderm, mesoderm and endoderm. A deficiency is rarely limited to but one vitamin. There can be no cure when there is no deficiency. Unless the tissues are actually destroyed, a deficiency state can be cured. One should not expect to improve hearing by regeneration of the eighth nerve unless the sensory apparatus in the internal ear is viable. In general, treatment should not be limited to vitamin therapy, but food should be given which provides an abundance not only of any one vitamin but of others as well. A vitamin is not a drug. Vitamin requirements of individuals vary greatly: some are unable to absorb vitamins, others cannot retain and utilize them. There are complicating factors as to dosage. Exercise increases the need for vitamins. While alcohol supplies calories to the body it contains no vitamins. A chronic alcoholic may therefore exhibit a desperate need for a large vitamin intake. Natural foods are rich in calories, minerals and vitamins but in refining and preparing these foods a considerable part of the vitamin content is lost. Though the calorie intake of an individual is often adequate, the vitamin intake is not. Generally, vitamin therapy should be continued over an appreciable length of time.

Wallner²⁰ reviews the clinical aspects of vitamin deficiency in ear, nose and throat and asserts that there is no special characteristic of infections involving these regions that identify it as due to lack of vitamin A. At the present time there exists no simple method for determining the presence of vitamin A deficiency. Blood level determinations or dark adaptation tests are not practical for routine office or clinic use. The administration of vitamin A to persons already receiving an adequate intake in the diet does not lessen susceptibility to colds. It may shorten their duration or lessen their severity. The term anti-infective vitamin is not justified. The status of vitamins B₁ and B complex is summarized as follows: There is no disease syndrome in the ear, nose and throat characteristic of vitamin B deficiency. It may be used empirically in nerve deafness, Ménière's disease, and in the troublesome and baffling neuralgias about the sinuses, throat and head. With the exception of scurvy, there are no characteristic conditions in these regions typical of vitamin C deficiency. Clinically, there is no evidence that a lack of vitamin D is a causative factor in otosclerosis or that its administration influences its progress.

According to Spiesman,¹⁶ vitamins A and D in massive doses for the treatment of the common cold do not produce immunity when given separately. When massive doses of vitamins A and D were given together, 80% of the subjects showed a significant reduction in both the number and the severity of common colds. The number of colds per year dropped to 3, and the average duration was 5 days, with but little elevation in temperature. It must not be assumed that the use of vitamins in the treatment of the common infectious cold is offered as a

panacea for colds. Average susceptibility must be taken seriously into account, as well as the emotional state of the subject as affected by an innately unstable vasomotor mechanism. Reviewing 1590 cases of diphtheria which were observed during 1936 and 1937, Feige⁶ found 100 cases in which postdiphtheritic paralysis developed. Of the 60 patients in whom the entire course of the postdiphtheritic paralysis could be observed, 30 were treated with a preparation of vitamin B₁ and 30 either received no treatment for the paralytic symptoms or were treated with other medicaments. A comparison of these two groups of patients revealed that in those who were treated with vitamin B₁ the paralytic symptoms persisted on the average for 29.6 days whereas in the other group they persisted on the average for 49 days. Vitamin B₁ was administered by mouth and by intramuscular injection on alternate days. On one day the children were given 3 tablets containing 1 mg. each of the vitamin; on the following day they were given an intramuscular injection of 1 cc. of a vitamin B₁ preparation. In discussing the pathogenesis of postdiphtheritic paralysis Feige cites observations of several investigators and suggests that these postdiphtheritic paralytic symptoms are the result of the concurrence of toxic impairment of the tissues and lack of the B₁ substance, which has a ferment-like action. He thinks that this explains at the same time the success of the treatment with vitamin B₁. Stinson¹⁷ declares that the primary obstructive factor in cardiospasm is the lack of propulsive force in the falls of the esophagus rather than obstruction at the cardia. Mosher's intrinsic findings can be the result of stasis in the esophagus and his extrinsic findings, the result of vitamin B₁ deficiency, rather than the primary cause of cardiospasm. Cardiospasm is frequently a manifestation of avitaminosis B₁. Vitamin B₁ given intramuscularly will relieve an attack of cardiospasm in many instances. Continued administration of vitamin B₁ will prevent recurrence of attacks of cardiospasm in these cases.

It is in the field of otology that vitamin research has attracted most interest. To determine the pathologic changes in the peripheral auditory mechanism due to avitaminoses, deficiency experiments on rats were done by Covell.⁵ Vitamin A deficiency was found associated with middle ear infections, increase in the periosteal layer of the otic capsule and occasionally exostoses in the internal auditory canal, degeneration of the cells of the stria vascularis, external sulcus cells and parts of the organ of Corti, with slight to moderate demyelination of the cochlear nerve. There is a higher incidence of middle ear infections in animals when vitamin B and various factors of the B complex are lacking in the diet. Avitaminoses of the B group cause no significant changes in the bone of the otic capsule or ossicular chain. However, spiral ganglion cells are altered in appearance in all avitaminoses of the B group and degenerative changes are found in the external hair cells of riboflavin-deficient animals. It appears that the three most important vitamins for the maintenance of the myelin sheath of the cochlear nerve are the B vitamins, thiamin chloride and riboflavin. Vitamin C-deficient guinea pigs display hemorrhage into the lining of the middle ear cavity, with an increase in the thickness of the submucosa. Only slight demyelination of the cochlear nerve is produced.

The cells of the organ of Corti and some of the cells of the stria vascularis become swollen and degenerated. A chronic deficiency of vitamin C may produce more extensive changes, particularly in the ossicular joints and the bone of the capsule. Rats, it is found, frequently have infections of the middle ear when they are deficient in vitamin D. Here, demyelination of the cochlear nerve occurs. Third generation rats on a low diet of vitamin E also show middle ear infections. Considerable fibrous tissue replacement of the muscle bundles takes place in the muscles of the middle ear, particularly the tensor tympani. Hemorrhages about the nerve in the modiolus and under the dura and submucosa of the middle ear occur in these animals. Loch¹⁰ has studied the changes in the labyrinth capsule, occurring as a result of experimental avitaminoses A, C, D and E, in the serial sections of 56 petrous bones of rats and guinea pigs. The earliest noticeable effects produced by avitaminosis A are small hemorrhages, followed by inflammatory and metaplastic changes in the mucous membrane of the middle ear. With the maintenance of a vitamin A deficiency over a period of several weeks, regular layers of new bone are formed by the periosteal capsule. In a few cases, small degenerative changes are detected in the auditory nerve. In avitaminosis C, hemorrhages also occur at first, and gradually the cellular marrow of the periosteal layer is transformed into fibrous marrow, with alterations or disappearance of osteoblasts. Consequently, there is a diminution of bony material. Bone changes take place in the periosteal layer. Avitaminosis D is characterized by deposition of osteoid tissue in the rarefied mature bone, and these changes are discerned in the periosteal and the enchondral capsule, while the endosteal layer is spared. Prior to the bone changes, suppuration of the middle ear was invariably found. In avitaminosis E, there is an irregular, localized new formation of mature bone with numerous, small exostoses in the region of the periosteal and the endosteal layers, while the enchondral layer remains unchanged. As accompanying features, suppuration of the middle ear and hemorrhages in the brain tissue were observed. Mellanby¹¹ reports his continued investigations in experimental deafness. He examined a total of 51 labyrinths from 44 dogs placed on a diet deficient in vitamin A for a period of from 2 to 4 months. He finds that the most obvious pathologic changes in the labyrinths are: nerve degeneration, especially of the cochlear neurons; new bony growths in the modiolus; overgrowth of the internal periosteal layer of the capsule; serous labyrinthitis; and degenerative changes of the organ of Corti and sensory epithelium of the semicircular canals. Perlman and Willard¹³ observed that young rabbits raised on a diet depleted of vitamin A develop extensive hypertrophy of the periosteal layer of the otic capsule on the cranial aspect, including internal acoustic meatus, posterior fossa surface and mouth of the flocculus. The overgrowth of mature lamellar periosteal bone in the internal acoustic meatus results in narrowing and elongation of the internal acoustic meatus with compression and stretching of the nerve fibers and Scarpa's ganglion in the meatus. In spite of this compression and stretching good cochlear function was retained. This was demonstrated by threshold studies on the acoustic middle ear muscle reflex. The compression and stretching of the nerve resulted

in various degrees of degenerative changes in some of the cells in the vestibular and cochlear ganglion, and in one case degeneration of the peripheral fibers to part of the basal coil. There was no evidence of serous labyrinthitis or of degeneration of Corti's organ, the vestibular end organs or the stria vascularis. The structures of the middle ear including the adjacent labyrinth bone were unaffected.

The possibilities of vitamin C management in cases of inner ear deafness and tinnitus are advanced by Szolnok¹⁸ who observed 50 cases of different cochlear disturbances. In individuals with chronic catarrh of the middle ear and otosclerosis, injections of vitamin C diminished the tinnitus. The improvement seen in cases of arteriosclerosis of the inner ear was due, this author asserts, to the general increase of metabolism. Two injections of vitamin C were administered weekly for 4 weeks along with a diet containing lemon. Improvement of hearing was present in 50% of the series of cases together with a decrease of tinnitus and blood pressure. In discussing the possibilities of vitamin C therapy in inner ear deafness and tinnitus, Baer¹ warns against drawing definite conclusions from Szolnok's cases because the original diagnosis of arteriosclerosis was not clearly defined. However, he agrees that ascorbic acid often causes a disappearance of tinnitus, particularly when vitamin C is employed in combination with vitamin B₁. Brandenburg² describes a case of severe bilateral tinnitus and impairment of hearing following extensive radiation therapy for carcinoma of the cervix uteri in which relief was obtained by daily intravenous injection of thiamin chloride in 10 and 15 mg. doses for 9 days. Intravenous administration of thiamin chloride in one or more daily doses of 10 mg. for all neuropathies of the cranial nerves is suggested. The nature of vitamin B and its components with special reference to nerve deafness is studied by Veasey¹⁹ who finds it has been impossible to formulate a definite clinical syndrome for mild vitamin B deficiency. A review of his own cases of deafness treated by vitamin B suggests there is a possibility of helping some individuals by this means, but at the present time there are no means of selecting the patients who may be improved. Langenbeck⁹ reports the complicated case of a child with bilateral otitis media who had undergone several operations on both ears because of recurrent attacks of otogenous meningitis but who finally recovered. He states that other factors beside the use of sulfanilamide and apical drainage played a major part in the recovery and points to the use of vitamin C which was administered by mouth. To study the relation of vitamin C to the mucosa of the middle ear Chimani⁴ examined 18 patients with chronic suppurative otitis media as to hypovitaminosis. He concluded that chronic middle ear suppuration may not be due to hypovitaminosis, but patients with this affection often have vitamin C deficiency, and in such cases the administration of ascorbic acid is a helpful therapeutic measure. The case histories of 4 patients with symptoms typical of Ménière's disease, who also had symptoms of hypovitaminosis A and C, are described by Morch.¹² The symptoms of hypovitaminosis A observed were conjunctival irritation, photophobia, pharyngeal and nasopharyngeal dryness, occasional irritation of the larynx, loss of appetite, painful respiration, loss of the sense of smell, periodic attacks of thirst, lassitude and listlessness,

lumbago and myalgia. The observed symptoms of avitaminosis C were gingivitis and irritation and redness of the buccal mucosa and the pharynx, saggillation of the legs, papillar eruptions between the fingers, intense lassitude and dyspepsia. Morch gave his 4 patients intensive treatment with vitamins A or C, as the case required, by intramuscular injection up to the point of producing hypervitaminosis. There was amelioration of the vertigo and tinnitus with improvement in the hearing of all 4 patients, but the author states that it is still too soon to determine the potency of the results.

An investigator deeply interested in the relationship of vitamins to nerve deafness is Selfridge,^{14a-d} author of four recently published articles. Because deficiencies of various vitamins—C, B₁ and the B₂ complex—have been found to produce degeneration of the eighth nerve in animals, he has employed large doses of vitamins with correction of unbalanced diets in cases of nerve deafness. In his first article, he reviews 6 cases given nicotinic acid for many months which resulted in audiometric improvements averaging 5 to 10 decibels throughout the tone range, but in some cases amounting to 15 to 25 decibels for the lower tones. In his second article Selfridge reports 6 cases of nerve deafness treated with injections of riboflavin, thiamin hydrochloride or nicotinic acid. In the first patient riboflavin produced no improvement, nicotinic acid produced a definite improvement in both ears, and thiamin hydrochloride produced no further improvement. In the second patient, nicotinic acid showed a hearing improvement in both ears while thiamin hydrochloride resulted in an additional improvement. Nicotinic acid prompted improvement chiefly in one ear of a third patient while thiamin hydrochloride improved the other ear. In a fourth patient continued improvement was observed with both preparations. Similar improvement was seen in a fifth patient. Nicotinic acid and riboflavin produced a slight gain in an elderly sixth patient, while thiamin hydrochloride produced no further improvement and continued use of nicotinic acid established additional gain. From these cases the author concludes that thiamin hydrochloride is an essential addition to nicotinic acid, but that the greatest improvement occurs following the use of nicotinic acid. In a third article the author describes the case of a 9-year-old child with unilateral high tone deafness of 3 years' duration following active otitis media. There was a slight audiometric improvement with the patient on a high-vitamin diet plus the vitamin B complex, carotene and vitamin C. An 18-year-old girl who had unilateral tinnitus and deafness for 18 months was given vitamin C, thiamin hydrochloride and nicotinic acid, with striking improvement in the tinnitus and deafness. In commenting on these three articles Shambaugh¹⁵ asserts that the strongest argument against the theory that vitamins are important in nerve deafness is the fact that deafness is not a symptom of clinical avitaminosis. Neither scurvy, beriberi nor pellagra have been shown to be associated with nerve deafness. While not convinced that vitamins are a factor in nerve deafness, he has attempted to maintain an open mind and has employed them in numerous cases of nerve deafness, with uniformly negative results to date. In his fourth article Selfridge reviews the literature on deficiencies of the various vitamins and the effect of these deficiencies on the function

of the eighth nerve and on the incidence and severity of infections. Lack of vitamins A, B or C apparently causes changes in the eighth nerve, in addition to other more general effects. Deficiencies in vitamins B and C appear to have a distinct bearing on certain allergic manifestations. All the vitamins are essential during acute infections; they do not shorten the infection but seem to aid in sustaining the general physical condition. The tendency to be subject to the common cold appears lessened if the diet contains all of the essential vitamins in sufficient quantity.

In a discussion of otologic research and its recent contributions to clinical otology, Hughson and Thompson⁷ sum up the rôle of vitamins in this field. They write, "There is no more completely disappointing phase of the therapy of deafness than the supposed effect of vitamins upon hearing. A critical analysis of the effect of vitamin therapy in human deafness begets a feeling of complete futility. From an anatomic standpoint alone, neural impairment of hearing is final and in its manifest and individual degree, complete. Why should vitamin B or any one of its various complexes restore function to an organ of Corti deprived of its neural mechanism? The sooner this misrepresentation is corrected the sooner the reputation for honesty of otologists and the peace of mind of the deafened individual will be achieved. Controlled vitamin experimentation in relation to deafness presents almost insurmountable difficulties. Only extreme anatomic effects are demonstrable experimentally. The intermediate phases of hearing loss, if and when they occur, are not a matter of record. It is most unlikely that any of the neurologic effects produced by extreme experimental lacks are significant from the standpoint of human clinical deafness. All reported results of therapy are inconclusive. There is no anatomic evidence that the anatomic result of dietary defects is corrected by appropriate vitamin replacement. At the moment it would seem that this entire subject is lacking in true scientific control which is possible only with animal experimentation. Any human audiograms, so far presented, are of no real significance if taken as a measure of the effectiveness of vitamin therapy."

NOAH D. FABRICANT, M.D.

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DERMATOLOGY AND SYPHILOLOGY.

UNDER THE CHARGE OF
JOHN H. STOKES, M.D.,

HERMAN BEERMAN, M.D., AND NORMAN R. INGRAHAM, JR., M.D.
PROFESSOR AND ASSISTANT PROFESSORS, RESPECTIVELY, DEPARTMENT OF DERMATOLOGY
AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA, PA.

PHOTODYNAMIC EFFECTS IN DERMATOLOGY.

PART I.

A RAPIDLY developing, evidently important field of dermatology and of medicine at large, such as that of the effect of light on the body, deserves periodic review and progress reporting, not because of the finalities that can be presented, but because of the value of theorization in promoting further advance. The first impression the observer gets of the field of photodynamic effect is that of the complexity of components and the exceptional range of knowledge required of the evaluator for a proper appreciation of the causal mechanism. It is proposed therefore, to divide this presentation into Part I, which will discuss photodynamic agents and mechanisms; and Part II, which will discuss the diseases with a prominent cutaneous aspect in which photodynamic effects appear to play a leading part.

Historical Background. Blum's volume,⁶² "Photodynamic Action and Diseases Caused by Light," the most recent and in fact the major contribution to the systemitization of this field, credits the observations of Oscar Raab,⁷² a student in the laboratory of Tappeiner at Munich, on the toxicity of acridine for paramecium as the starting point of the modern study of photodynamic phenomena. Raab found that the intensity of the toxic action of the dye on the unicellular organism was proportional to the intensity of light in the laboratory. To the dermatologist, the modern study of light sensitivity as affecting the skin begins with Meyer-Betz's⁶⁴ observation in 1913 of the near-disastrous effect on himself of an intravenous injection of 0.2 gm. of hemato-porphyrin, the substance previously identified in the urine of the photodynamic dermatosis, *hydroa aestivale*. Exposure of a portion of Meyer-Betz's skin to a Finsen lamp 15 minutes later resulted in conspicuous swelling, deep infiltration and hemorrhagic necrosis of the whole exposed cutis. Two days later, a short exposure to the sun resulted in immediate and severe reaction. Meyer-Betz was still sensitive to light 2 months after the injection, although the porphyrin itself could no longer be detected in the blood serum 3 days after injection. Simultaneously with Raab's observation on paramecia, Prime⁷⁰ described what appear to have been photosensitive reactions in epileptics injected with eosin, used because of its bromine content. Following Raab's initial observation, attempts were made to use eosin to increase the effectiveness of treatment for lupus vulgaris, but without notable success. Jausion and Maceron⁴⁵ in 1925 accidentally rediscovered the photosensitizing action of acridine compounds when treating soldiers with

trypaflavine for gonorrhea; and another sporadic application of dyes to light therapy ensued. Haxthausen's case^{35b} in 1933 indicated that prolonged effects, such as Meyer-Betz observed in his own case with hematoporphyrin, may be due to an intrinsic constitutional background factor "set off" by the photosensitizing agent. Photosensitization by direct application of substances to the surface of the skin seems to have had its clinical birth with the observations of Freund²⁹ on berloque dermatitis (1916). The ingredient of toilet waters and perfumes probably responsible for a markedly pigment-producing dermatitis on exposure to sunlight is oil of bergamot (Blum). Oppenheim^{68a,b} in 1926 found a dermatitis occurring in persons taking sunbaths after contact with certain meadow plants. From these beginnings the study of photodynamic effect on the skin has proceeded on the one hand toward an increasing list of substances, following contact with which the surface of the skin becomes sensitized to light and an increasingly intensive study of the porphyrins as metabolites largely instrumental or at least associated with cutaneous and constitutional photodynamic effects. Between the two groups of investigation have labored the physicists and near-physicists, who have attempted to analyze the action of light in terms of its physical components, spectrum and wave lengths.

The Components of the Problem. In the literature of today there are recognizable accordingly five distinct groups of observations contributory towards our growing understanding of photodynamic phenomena. The first identifies and lists the exogenous and endogenous *agents*. The second deals with studies involving the composition of light. The third deals with the analysis and interpretation of the local cutaneous reaction to light; the fourth with the sources and genesis of endogenous photosensitizers, this latter to be considered with the first group; and the fifth, with the systemic, bacterial and vitamin contributors to photodynamic effect.

The Exogenous and Endogenous Agents. The term "exogenous," admittedly not fully satisfactory, requires subdivision into photodynamic or photosensitizing agents acting by topical or external application and photosensitizing agents parenterally introduced either by ingestion or injection. The seat of application in externally acting photosensitizers as Guillaume^{33a,b,c} has shown is the Malpighian layer of the epidermis, no photodynamic response occurring unless this layer is exposed by abrasion or otherwise to the action of the substance. The following list includes most of the substances, many of them as will be seen in the category of dyes or essential oils which are now known to have photosensitizing properties. Sandler,⁷⁸ Kuske^{52c} and Blum^{5a} have compiled similar lists.

Essential Oils.^{5a} Oil of citron,¹⁶ oil of bergamot,^{29,31,75} oil of lavender, oil of cedar, vanillan oils, lime oil,⁷⁷ oil containing perfumes (Eau de Cologne).

Plants and Plant Substances.^{5a,b,41,52a,b,58,68a} Chlorophyll,^{50a,b,c} buckwheat (fagopyrism),⁶³ clover (trifoliosis), Sudan grass and other grasses,⁷⁴ Hypericum (hypericism), Agave (lechuguilla), Tribulus (geeldikkop), Dictamnus albus (gas plant),¹⁵ meadow grass,^{14,43,44} fig plant,^{3,50a,b,c,91} Pastinaca sativa (parsnips),^{40,46} Ruta graveolens.^{52a,b,c}

Dyes. Eosin and eosin compounds,^{36,37,47,70} rose bengal,⁴⁷ erythrosin (fluorescein),⁴⁷ acriflavin,⁴² fabrie dyes,²¹ aeridine dyes (see below, coal tar), methylene blue, trypaflavin.^{35b}

Drugs. Sulfonamides,^{4,5c,9,20b,21c,22,27,57,65,67,73,80,86,92} barbiturates,^{69,84} gold,^{12,79} silver,³⁸ arspenamine.⁴⁹

External Medicaments. Coal-tar and petroleum products^{24,25,45,54} (see also acridine), green soap,^{2,71} mercury bichloride,^{48,11a,49} copper (?).^{30a,b}

Bacteria.^{20c,32}

Theorization on the action of the exogenous photodynamic agents began when Tappeiner⁶⁵ noted that washing out the sensitizing substance from the cell after a short exposure greatly weakened the resultant reaction to irradiation, but established the fact that biologic changes in the cell continue after the termination of the light exposure, suggesting that something in the cellular tissue fixed or absorbed the specific energies of the light employed. Neuberg compared the action of light sensitizers to that of metallic catalyzers, and stated that the effect of many of the dyes could be reproduced by organic catalysts such as iron, magnesium, cerium and uranium. Eidinow^{20a} showed that the volume and concentration of the fluid suspension irradiated was influential in the effect; that the concentration of chemical sensitizer present was a factor; that the intensity of luminous rays, the distance from the source of light and the temperature all contributed to the reaction. In studying the action of light sensitizers on bacteria and unicellular organisms it appeared that each sensitizer has a selective group of radiations at which a maximal biologic action ensued. Eosin, for example, is most active under yellow and orange visible rays; hematoporphyrin has a maximum action under blue and violet irradiations. The bactericidal action of many substances was found to be increased by light. The extensive theoretical considerations of Blum^{5a} indicate a close association of the photosensitizing mechanism with the oxidation mechanism of the cell. Eidinow found that blood serum acts as a protective agent against light sensitizers as well as a diluent of their concentrations. Washed (serum-free) red blood cells suspended in saline are readily hemolyzed by light in the presence of a sensitizer—a valuable index of photosensitizing power. Human leukocytes are likewise readily destroyed by light in the presence of sensitizers (eosin). Eidinow's work indicated that fluorescent radiation of a group of substances not ordinarily productive of light-sensitizing effect would convert them into light sensitizers. Eidinow's work further tended to align the biologic action of light sensitization with that of ultraviolet irradiation effect, using rays of wave lengths shorter than 3100 A.U.; in other words, an intensification of, or a selective emphasis on, ultraviolet effect.

Endogenous Photodynamic Agents (Porphyrins). The endogenous photosensitizing agents thus far recognized belong to a complicated chemical group—the porphyrins. Hematoporphyrin, with which the study of these agents began is an artificial or synthetic porphyrin not found in Nature. It was at first described as iron-free hematin, a degeneration product from hemoglobin. The photodynamic properties of hematoporphyrin are now largely of theoretical interest, but occasionally appear as complications of the therapeutic use of photodynamic (proprietary hematoporphyrin preparation).

American students of the medical phases of porphyrin metabolism will find extensive consideration of the fundamentals in the publications of Dobriner and his associates,^{17a,b,18,19} and in Blum's valuable mono-

graph.^{5a} Important contributions to photodynamic phases of cutaneous disease involving porphyrin metabolism have been published by McFarland and Strain,⁶⁰ Brunsting, Brugsch and O'Leary,^{8,10} Blum and Pace,⁶ and Turner and Obermayer.^{87a,b,88} The clinician's desire to be able to put his index finger on the sole chemical cause and his inability to satisfy it in the case of porphyrins will be apparent by a study of the complexity of these pyrrol compounds. Fiseher,^{23a,b,c} working on the first case of chemically studied congenital porphyria, identified two different pigments in the excreta; uroporphyrin, found only in urine, and coproporphyrin, found in both urine and feces. It is now known that small amounts of the coproporphyrin are found in normal urine and feces, but that the uroporphyrin is a pathologic product excreted almost exclusively in congenital porphyria. As Dobriner and Rhoads^{17b} point out, these observations constituted the beginning of elaborate chemical studies which have shown that uroporphyrin and coproporphyrin as above described differ fundamentally from the protoporphyrin actually identified in hemoglobin. Porphyrins have been identified in yeast likewise, and it has become clear that there exist side by side in the complicated chemistry of the porphyrins, isomers which have entirely different properties and very possibly different origins, notwithstanding that they all are regarded as derivatives or products of the destruction of the respiratory pigment.

The porphyrins which appear most frequently in clinical nomenclature include uroporphyrins I and III, found in the urine of human beings with congenital porphyria, and in the bones of certain animals,^{87a} and coproporphyrins I and III, present during health in small amounts in the urine and feces. The predominating porphyrin in both excreta is coproporphyrin I, with extremely small amounts, or traces, of coproporphyrin III and occasionally of uroporphyrins I and III. The level of excretion of total porphyrins determined by extraction from the urine and feces may be taken as from 300 to 400 $\mu\text{g.}$ per day of which 30 to 70 $\mu\text{g.}$ is excreted in the urine. In diseases involving dysfunction of the pigment metabolism the amount of porphyrin excreted may increase or decrease, depending on the nature of the disease. For example, in pernicious anemia and pellagra, the level of excretion is several times normal, while in von Jaksch's and in secondary anemia the level of excretion is much less. With increased excretion of porphyrin there may be gastro-intestinal disturbances, dysfunction of the nervous system and cutaneous abnormalities.

For the clinician desirous of using conceptions based on porphyrins in his causal theorization, certain elementary principles are important. Porphyrins are definite chemical compounds, chemically identifiable by the usual criteria of spectroscopic analysis, melting point and so forth, and they should be positively identified in any form of investigation expected now or in the future to have etiologic significance. A lack of constancy of the appearance of a particular porphyrin in one or another of the excreta suggests as much as anything else that porphyrins are not necessarily the basic cause of the conditions in which they appear but are by-products with photosensitizing effects. The question as to whether such photosensitization is a direct interaction between the photodynamic porphyrin and the reacting cell is anything but settled, and the presence of intermediate mechanisms may properly be sus-

pected from the fact that notwithstanding the presence of these substances in abnormal amounts in the excreta, patients may fail of photosensitization. In the light of these considerations, the mere reporting of increased amounts of any particular porphyrin in one or the other of the excreta, or the increase or decrease in the amount excreted under any form of treatment no longer satisfies the requirements for a causal analysis.

The porphyrins commonly encountered clinically vary considerably in their photodynamic power. Coproporphyrin type I sensitizes less than uroporphyrin type I, and the effect of uroporphyrin type III has not been studied. Coproporphyrin type III produces less light sensitivity than does coproporphyrin type I. The destruction of porphyrins in tissues has been studied, and it would appear that liver tissue, at least *in vitro*, participates in the destruction of such substances as hematoporphyrin. Coproporphyrin type III apparently appears when the liver is perfused with solutions of protoporphyrin in defibrinated blood. Coproporphyrin I and uroporphyrin I increase the tonus of the intestinal tract, the effect not being abolished by atropin. Indications of premature follicle formation in the ovaries of infantile mice were recognized by Hinsberg³⁹ following injection of hematoporphyrin and protoporphyrin.

In the reading of the clinical literature on porphyrins, it should be pointed out that the inexperienced should not confuse the total amount of coproporphyrin excreted in 24 hours in both stools and urine (300 to 400 $\mu\text{g.}$)⁷ with a specific amount per 100 cc. of urine of a random specimen of urine.

Those interested in the simpler methods of quantitative laboratory determination of coproporphyrin III especially should consult a discussion by Dobriner and Rhoads,^{17a} dealing with this question. As an indicator in some affections of the liver and some toxic states, and a gauge either of increased total production of the coproporphyrins or a liver insufficiency of such a degree as to divert coproporphyrin into the urine with consequent disturbance of the urinary-fecal ratio, these simpler methods may prove to have special clinical interest.

The Composition of Light. Despite the fact that all critical recent observers have pointed out the shortcomings of reports in which neither the constancy of the light source nor its character in terms of wave lengths is definitely known, clinical statements with regard to photosensitiveness are still being made without any accurate knowledge on these points. In order to make available to the clinical observer some concrete statements of the composition of light from the sources that he is likely to employ in tests and treatment, several tables have been devised, including those of Krusen.⁵¹ The Reviewers have prepared Table 1, given herewith from various sources in the recent literature.

Since there is thus far no reason for discarding the belief that the fundamental fact of photodynamic behavior is an absorption of a specific wave length of light by a photodynamic substance, there must be available against this inevitably somewhat confused and polystructural conglomeration of light sources a filtration scheme of some kind which will enable the clinical tester to feel reasonably certain that he is testing his patient with known type or wave length of light from

TABLE 1.—DISTRIBUTION OF SPECTRA FROM IMPORTANT SOURCES OF RADIATION USED IN PHOTODYNAMIC LITERATURE.

Source.	Peak or maximum intensity, A.U.	Range, A.U.	Remarks.
Sunlight at the earth's surface	4800 to 5200	About 2900 to about 18,500	Intensity and spectral distribution of sunlight vary with the seasons of the year because of difference of distance of sun from the earth, and difference in the thickness of the earth's atmosphere through which the radiation must pass. Water vapor, clouds, smoke and other variable factors modify sun's spectrum.
500-watt tungsten filament lamp (Mazda)	7700 to 12,000	About 3000 to more than 45,000	The tungsten lamp is to be distinguished from the S-1 type of lamp. (About 30% is of those wave lengths which can penetrate deeply into the skin.) Subject to much variation with the current, temperature and smudging of lamp. About 6% of total emission is of wave lengths shorter than 2900 A.U. which are absent in sunlight. They have high germicidal action.
Hot quartz mercury vapor arc, air-cooled	Line type, 2970 and 3020	Strong emission lines at 2570, 2650, 2800, 2970, 3020, 3130, 3340 and 3650, superimposed on faint continuous spectrum extending into infra red	Wave lengths around 2540 do not penetrate deeply in skin. Overexposure needed for erythema. Emits rays highly germicidal but which destroy vitamin D.
Cold quartz ultraviolet lamp	Line type, 2537 (95% of radiation emission)	Strong emission lines at 2540, 2970 and 3130	Many factors modify output; size and kind of electrode, direction of and amount of electric current.
Carbon arc	Band (continuous) type with range between 3500 and 4300 (Blum)	Depends in part on kind of carbon and other factors (see remarks). Principal emission is in the ultraviolet between 3500 and 4300 (Blum)	Nearest unscreened source to sunlight but is still "far from it."
1. A or sunshine carbon (impregnated with rare earths)	Strong emission band at about 3980	2200 to more than 4000	
2. B carbon (impregnated with iron oxide)	Ultraviolet radiations of less than 3100 exceeds that of other carbon arcs listed		
3. C carbon (impregnated with calcium oxide)	Also strong emission from 5000 to 7500	2200 to more than 4000	
S-1 ultraviolet lamp (combination of mercury arc between highly incandescent tungsten electrodes in parallel with tungsten filament in bulb of special glass)	Line type, 2970, 3020, 3130	Strong emission spectrum of lines at 2800, 2970, 3020, 3130, 3340, 3650, 4050, superimposed on continuous spectrum which increases rapidly in intensity from 3650 and extends deeply into the infrared	At 3 feet intensity about equal to about 1/10 to 1/15 solar radiation.
S-2 ultraviolet lamp	Never model. Ultraviolet radiant flux is such as to give practically the same as the ultraviolet in midsummer midday sunlight (patient 2 feet away from lamp).

Adapted from statements in Blum, H. F.: Photodynamic Action and Diseases Caused by Light, New York, Reinhold Publishing Corp., 1941; and Coblenz, W. W.: in Handbook of Physical Therapy, American Medical Association, Chicago, 1932.

the source he is able to use. Urbach and Konrad, for example, in 1929⁹⁰ proposed a simple subdivision of light with which they investigated the photodynamic sensibilities of a case of prurigo æstivalis Hutchinson, and the light-protective effect of resorcin. They employed red, yellow and green glass filters, and found the sensitivity of their patients to be to the rays passed by the yellow and red, and accordingly lying in the wave lengths between 4900 and 7000 A.U. More recently McLoughlin and Krusen⁶² have better defined the means by which certain known wave lengths of light from the carbon arc B carbon as a constant source can be secured for test purposes. The description accompanying their diagram is as follows:

"The five successive portions of the spectrum to which the skin is exposed:

"(1) Unfiltered radiation from carbon arc lamp employing 'B' carbons.

"(2) Carbon arc radiation through a Corning No. 774 filter.

"(3) Carbon arc radiation through a Corning No. 396 filter.

"(4) Radiation from a 250-watt Mazda CX lamp through a Corning No. 255 filter.

"(5) Radiation from a non-luminous coil type of infra-red burner." (The latter placed in a polished reflection.)

The procedure which they described is as follows:

"The portion of skin to be tested is exposed to one minimal erythema dose of unfiltered rays from the carbon arc lamp. All the surrounding skin is covered with toweling. Prior to exposure the areas to be tested may be outlined with a pencil for skin marking for purposes of identification. The test is repeated in another area with filter Number 774, covering the area of skin exposed to the arc. One erythema dose is applied. This filter prevents transmission of that portion of the spectrum which contains the rays producing sunburn. The third area is exposed to the carbon arc lamp, using a Number 396 filter. This supplies some ultra-violet and invisible light, and eliminates almost all heat rays. The fourth area is exposed to the rays of a Mazda CX therapeutic lamp, using a Number 255 filter. This filter transmits only the near infra-red portion of the spectrum and none of the visible rays. The last area is exposed to the infra-red burner which produces no visible rays, but only the far infra-red radiation. The last two exposures are of five minutes' duration at a distance of approximately 18 inches (46 cm.) or at a distance at which the rays can be tolerated by the patient without causing discomfort."

There is no statement as to what constitutes an erythema dose, which presumably must be learned by experience. There is, moreover, reason to believe that the size of the openings through which the dose of actinic light is administered affects the grade of reaction, and must for this reason be kept constant. Blum⁵⁴ points out other factors (chiefly described by him in connection with susceptibility to cancer on the face) of which account must be taken in light or photodynamic testing, such as the embryogenesis of the exposed skin as suggested by McFarland, Ciccone and Gelehrter⁶¹ and the thickness of the epidermis, as affecting the penetration of light. For example, Lucas⁵⁵ found that wave lengths of 3000 A.U. are 44% transmitted by epidermis 0.08 mm. thick, while less than 5% of wave lengths 2900 A.U. and shorter are

transmitted by this thickness. Bachem and Reed's¹ values were even lower. Repeated exposure to light, by affecting the thickness of the stratum corneum (Miescher⁶⁶) will further influence the effect of successive tests, and is the probable explanation of decreasing sensitivity to light on repeated exposure rather than its conventional explanation as due to accumulated pigment. It would appear therefore that necessary constants in comparable tests should be a selected part of the body, a part of constant size, and a selected interval between successive exposures.

Haxthausen^{35a} has pointed out that vascular changes and permanent dilatation follow the action of sunlight and cold, and that these may be factors influencing the response of covered and uncovered portions of the body to light test procedures. Chemical injury, particularly by tar and dust carcinogens and possibly also contact allergens, must furthermore be taken into account in individual subjects.

The distinction between blondes and brunettes, often emphasized in interpreting reaction to light, is far more difficult of description than the casual observer would expect. It is obviously necessary to have some standard method of expressing the color of the skin which is a compound of vascular distribution and blood content, and intrinsic (melanin) pigmentation before proceeding to describe a light reaction in accurate test terms. The interaction of exposure to light and exposure to temperature in modifying both the vascular and the pigment factor increases the complexity of this descriptive element in a uniform test, and it cannot be said that present knowledge suffices, without further study, for an accurate definition.

Blum^{5d} believes that the mere intensity of pigmentation in the brunette is hardly a trustworthy single index of susceptibility to ultraviolet radiation, notwithstanding the belief of competent investigators, including Miescher,⁶⁶ that pigment, especially in the negroid type, is an important element in their relative insusceptibility to the ultraviolet. A fair search of the literature has failed to identify any authoritative definition of blondness *versus* brunetteness. MacKee⁵⁶ in the first edition of his pioneer text, in the days when unfiltered Roentgen ray for skin therapy was standardized by physiologic testing of the erythema dose on the human skin, could give no clearer definition of a proper subject than to specify that one "utilize a split pea sized area of skin on the flexor surface of the forearm of a female adolescent (preferably a blonde) for the experiment. . . . The reason for selecting a young fair skin and a flexor surface is because such skin is more sensitive than dark skin in the extensor surface of older individuals."

It would appear therefore that before we have an accurate measure of photodynamic effect suitable for comparisons, it will be necessary to develop beyond the present accuracy and availability, spectrophotometric apparatus for analysis of the color of the skin. Attempts have been made to use "color wheels," permitting comparator estimations of the color of a rotating disk with that of the skin, to the percentage analysis of the component colors in the disk (Rowntree and Brown⁷⁶). Such instruments as the Macbeth illuminometer can with modifications measure the light reflected from the skin surface, but it is doubtful if these will satisfy the requirements. Published studies by Rogin and Sheard⁷⁵ describe an analysis of the color of the skin following irradiation.

tion by ultraviolet rays, using spectrophotometric equipment developed by Sheard, but too complicated for extensive use, especially under clinical conditions. Such apparatus has, however, contributed materially to the understanding of the "erythema" behavior of the skin as a physiologic reaction. It must be clear, therefore, that not only with respect to accurate statement of the composition of the light source concerned in photodynamic action, the whole subject of photodynamic effect requires a basic investigation of essential standards for test methods, including the response of the test tissue (skin) itself.

The Local Cutaneous Reaction to Light. The basic work in this field has been done by observers of radiologic erythema effect, including Miescher⁶⁶ and Sheard. Without going into the technical details of the methods used by the latter which should be studied in the original publications, many interesting sidelights appear concerning the control factors, including area of irradiation, posture and so forth, which should be studied by users of tests. From the first it was apparent in Rogin and Sheard's⁷⁵ work that the reaction of the skin to light has a cyclical or crisis-like character under all of the wave lengths tested in Roentgen, ultraviolet and visible spectrum fields. The meaning of this cyclical reaction is not apparently as yet clear, but the associated pigment production and so on affects successive exposures and tests. Similar wave-like phenomena in erythema reactions have been identified in mustard oil dermatitis and are believed to exist in tuberculin reactions and so forth. Wide individual variations in the cyclical or crisis reaction are recognized, both as to degree, latent period and other elements. The rhythmic or wave-like response to ultraviolet light persists for weeks following a single exposure. The formation of pigment also follows a rhythmic course, apparently independent of the course of the erythema. While the effects of the light exposure are evidently to some extent upon the vascular bed of the skin as well as upon the epidermis and pigment-bearing cells the cyclical character of the reaction does not seem to be wholly explained by these considerations. Laurens⁵³ has summarized some of the varied vascular effects of irradiation by sunlight. The curve of the first effect (hyperemia) indicates active arterial bloodflow. Later the curve shows the shift from oxyhemoglobin to reduced hemoglobin, indicating blood stagnation and decreasing local blood volume. An increase in melanin is indicated by depression of the violet end of the spectrum. The degeneration of melanin produces an allied pigment, melanoid, shown by a flattening of the curve near 400 m. μ . It has been recently pointed out that sex hormones have a significance in tanning which may be a photography-like process of exposure and development, with the sex hormone acting to develop color-lacking material laid down in the skin by exposure. Individual variations in the degree of pigmentary alterations during pregnancy may also be related to characteristic differences in the metabolism of the sex hormonal steroid. A film of sweat, containing dissolved or suspended substances, partially screens the skin against erythema-producing radiation. Many of the substances for which protective claims are made are valueless. Rogin and Sheard⁷⁵ demonstrated the absorption effects of the known light sensitizer, oil of bergamot, pure and in alcoholic solution, in studying the effect of ultraviolet light. The erythema was definitely *least* at the 5-hour interval after exposure in the surface treated with oil of bergamot, which

seems curiously out of keeping with the clinical belief that it acts as a photosensitizer.

The now generally accepted concepts of the H substance mechanism of inflammatory and erythema response in the skin (T. Lewis) makes particularly interesting the question as to whether light sets free histamine-like substances in the skin. In Laurens⁵³ review, citation is made of the fact that the unstable enzyme which converts histadine into histamine in animal tissues has been described, and evidence direct and indirect has been presented that ultraviolet irradiation increases the amount of H substance in skin and blood. Ultraviolet rays exert an inhibitory influence on the cutaneous reaction produced by intracutaneously injected histamine in non-allergic subjects but increase the reaction in allergic subjects, due to their constitutionally lowered ability to elaborate histaminase. It is suggested that the nature of the tissue injury caused by radiant energy resembles the effect of coagulation necrosis by mercuric chloride, and is different from that produced by venoms and staphylococcal toxins. From an analysis of the erythema curve and the pharmacologic action of ultraviolet radiation, there seems little room for doubt that an active substance is liberated which is responsible for the erythema response as an indirect capillary reaction. Apart from the vasodilation which appears after a latent interval, the structural changes are limited almost entirely to the stratum mucosum. The erythema response is due to the photochemical decomposition of some constituents of these cells with the liberation of active reaction products, which then diffuse to the region of the minute vessels of the subpapillary venous plexus of the corium and lead to vasodilation. The probable chemical nature of the photolyte is suggested by several independent lines of evidence. Consideration of its properties provides strong experimental support for its identification as a typical protein or a simple derivative. The hypothesis that the H colloid is to be identified with protoses formed photochemically offers a possible explanation of a number of the observed phenomena of the action of ultraviolet irradiation.

On the other hand, Laurens⁵³ states that observations on a case of urticaria solare, as cited, lead to the conclusion that neither histamine nor a readily diffusible H substance of low molecular weight is responsible for the skin response to ultraviolet irradiation. Attention should be drawn to the fact that there is in dermatologic conceptions at least a fundamental difference between the reactivity and excitation of reaction of the vascular structures of the skin, as contrasted with the epidermal structures. The epidermal dermatitic or inflammatory reactions partake more of the nature of a specific allergic effect on the basal layer of the epidermis. For more elaborate treatment and résumé of existing knowledge of the mechanism of light action on the skin with special reference to histamine, reference should be had to Blum.⁵⁴

What might be designated as grades of irritative response of the skin to the action of light is in need of further study both clinically and histologically. It is apparent that photosensitizers differ in the types of structures which they select (pigment, vessels, endothelium, Malpighian cells [basal cells] and so forth) in their photodynamic action. The rate at which reaction develops and the preponderance of certain elements (scaling *versus* erythema and vesiculation in different wave lengths and

compositions of light from various sources, hot *versus* cold quartz lamps and so forth) indicate the need for much study, before interpreting the specific modes and zones of action of photogenic substances. The discussion of carcinogenic effects in this connection is postponed to Part II. Authorities such as Blum^{5a} are inclined to minimize the biologic selective action in human tissue of certain wave lengths for certain structures, but this conclusion would seem to be the result as much of insufficient investigation as anything else. All authorities agree that one general category may be distinguished from all others. This comprises a group of destructive effects produced by radiation shorter than about 3300 A.U. From the high incidence of such effects a loose generalization may be made that such irradiation is, as a rule, destructive to living systems. It causes sunburn in man; and in other large animals produces effects varying from mild irritation to severe surface lesions. In some cases the effects of such radiation are stimulative rather than destructive, as with many destructive agents when acting in mild degree. The action spectra for bacteria, yeasts, dermatophytes, protozoa, bacteriophage and so forth, resemble the absorption spectra of egg albumen serum and other protein substances. The maxima of the action curve differ, for example, however, as much as 200 A.U. for protein and for nucleic acid. Bactericidal and fungicidal rays have action spectra resembling the absorption spectra of nucleic acid while those producing artificial parthenogenesis of the echinoderm egg and inactivation of pinworm eggs resemble the absorption spectra of protein. Sonne⁸¹ has suggested that a lipid substance in the red blood cell determines the hemolysis under the characteristic action spectrum. Still further evidence, again minimized by Blum's^{5a} discussion, that the action spectra of different wave lengths may have markedly differing biologic effects is recognizable in Flint and McAllister's²⁵ study (quoted by Blum^{5a}) indicating that three distinct action spectra take part in the inhibition and promotion of germination of dormant lettuce seeds. In this study there is suggested the possibility that photogenic effects may include the neutralization of one substance by another substance developed at a slightly differing wave length, and thus the canceling out or "antagonism" of one or another photogenic wave length of light by the action of another. The application of these considerations to the study of the skin is thus far practically *nil*, but account should be taken of their existence in estimating future trends and possibilities of investigation.

From the varied and not too clearly defined statements of several summaries, it appears that probably the most important factor in the local reaction of the skin to light irradiation is the ability of various wave lengths to penetrate to certain depths and excite certain groups of cells in the epidermis and cutis. The ultraviolet rays necessary for the prevention or healing of rickets, and the production of erythema, are those below 3200 to 3130 A.U. Lamps whose ultraviolet output ranges around 2900 A.U. with additional bands around 2600 and 2650 A.U. give only a fleeting erythema with a strong bactericidal effect. Coblentz and Stair¹³ concluded that maximal erythema production occurs at 2500 and even more intensely at 2950 A.U. with a minimum of erythema production at 2800 A.U. The erythema effect disappears entirely beyond 3300 A.U., and is almost zero at 3200 A.U. It should be realized therefore that the less circumscribed erythemas produced

by longer wave lengths than 3200 A.U. are heat effects apparently on the blood-vessels, and not the specific or sunburn erythemas produced by rays that do not pass beyond the Malpighian layer and hence are expressive of indirect blood-vessel effects (*via* the H substance mechanism). Mayer⁵⁹ states that erythema production occurs in the germinal layer or the corium under the shadow of the upper layers, and that absorption by the stratum corneum is so marked that it is practically impossible for irradiation between 2500 and 2000 A.U. and certainly of less than 2000 A.U. to reach the living layers of the skin and produce sunburn reaction. He further points out that sensitization with such substances as eosin and hematoporphyrin increases the effect of infra-red invisible rays which ordinarily are unable to produce destructive effects but merely cause dilation of superficial capillaries and increased bloodflow and exudation of lymph. The temporary "heat erythema" is not strictly local, in contrast to the delayed or true sunburn erythema which is limited sharply to the exposed area due to the local tissue changes of the nature of degeneration of the prickle cell layer which results in capillary stasis, diapedesis of leukocytes and other signs of inflammation to the degree of blistering. All these latter effects as above indicated are being more and more regarded as part of the Lewis H substance mechanism. The pigmentary changes on the other hand seem independent of the erythema to a considerable degree, since the pigment begins to appear before the erythema disappears and apparently depends on the intensity and duration of exposure. Blum^{5a} however, takes the view that the erythema and pigment-production mechanisms are identical, so far as action spectrum is concerned, and contests Frankenberger's²⁸ suggestion that the sunburn spectrum is made up of two parts—erythema production corresponding to the absorption spectrum of histidine, and pigmentation to the absorption spectrum of alkaline tyrosin. Blum^{5a} explains pigmentation on the basis of cell injury and believes the effect can be equally obtained by other noxious factors such as heat, chemical or mechanical injury and so forth. None of the hypothetical considerations thus far available provides a completely satisfying explanation of the pigment response to irradiation. The understanding of some of the pigmentary effects of externally applied photosensitizers such as perfume (Berloque dermatitis) must therefore await a fuller comprehension of the light-pigment mechanism.

The necrosis-producing effect of light is generally considered to be more a function of dosage than of wave length. It should be pointed out, however, in considering photogenic substances that in the reported cases of porphyria, quite extensive skin necrosis on exposure to light seems to be a rather characteristic reaction, and tends to indicate that the combination of light and certain photosensitizers has a necrotizing effect over and above that possible through light acting alone or upon unintoxicated tissue.

The antibacterial effects of light are generally accepted as being exercised by wave lengths below 3300 A.U. reaching a maximum intensity between 2600 and 2700 A.U. It seems to be most commonly believed that the bactericidal effect is direct and part of the destructive action of light as such on the protoplasm or chemical structure of bacterial cells. That this view does not embrace the entire range of

possibilities is certainly suggested by the work of Stevens,⁸² who in a series of carefully controlled experiments summarized by Krusen⁵¹ showed that bactericidal effects in the skin are mediated at least in part by peroxides developed from the oxidation of lipid substances and oils in the skin. Krusen states that there is no reason to believe, as has been suggested by some, that the rays are absorbed by oils and later are liberated as such. This statement refers to experimental work done on liquid petrolatum.

Laurens⁵³ in his recent summary cites the photodynamic action of dyes on antibodies. Dyes such as methylene blue, for example, destroy antipneumococcal serum in the presence of light. Neutralization of diphtheria toxin is inhibited after an exposure of mixed antitoxin and methylene blue to light. On the other hand, erythrosin and dizyanin-A sensitize bacteria to long-wave luminous energy and to the infra-red. Blum⁵⁴ further suggests that substances such as porphyrins and lactoflavin, present in small amounts in all living systems, may under intense light, develop important destructive or bactericidal action. Enzymes including peroxidase can be inactivated by short-wave lengths of light. The hemolytic effects of light are attributed to the presence of small amounts of protoporphyrin in red blood cells rather than to any known effect of light upon hemoglobin as such.

It seems reasonable to include among the constitutional effects which may accompany the antibacterial action of light, injuries inflicted upon the body, either directly toxic or as allergic effects, by the decomposition products of the bacteria which are destroyed by light. Clinic observation of light effects in susceptible subjects, particularly following sunburn in allergic individuals, suggests that the lymphadenopathy, muscle tenderness and occasionally joint symptoms produced following a sharp sunburn exposure may be in a sense "vaccine" reaction following irritation of bacterial foci and destruction of organisms in such foci by bactericidal substances developed in the skin and passing from thence into the circulation following light exposures. Thus far such conceptions are no more than theorization.

A line of differentiation in light effects should be drawn between the toxic action of light and its allergic effects, or action as an allergen. This differentiation has been defined so far as possible by Stephan Epstein^{21b,22} and Blum^{54,22} in published correspondence. Using sulfanilamide as a light sensitizer for the basis of the discussion, the contentions seem to resolve themselves into a matter of degree rather than of kind, in that they concern primarily excessive reactivity and to small amounts of the contributing agents, rather than a question of the actual existence or non-existence of such effects. Blum is inclined to oppose the introduction of terms other than "photodynamic effects" while Epstein, as a dermatologist and allergist, is inclined to rate the extreme grades of photodynamic effect as an expression of hypersensitivity, while allergy is, by the usual definition, "any specifically acquired alteration in the capacity of living tissue to react." Epstein insists that while the primary sulfanilamide light sensitization response is not an example of photodynamic action, the secondary sulfanilamide response described in his paper on photoallergy and primary photosensitivity to sulfanilamide, does not meet the requirements of allergy definitions. Blum, in virtual agreement with Epstein, accepts the secondary

sulfanilamide response as allergic, but insists that photosensitivity induced by rose bengal, abnormal sensitivity to blue and violet light, photosensitivity resulting from sulfanilamide injections, and even some examples of the repeated injection of sulfanilamide on irradiation response in human beings, shall not be swept into the same allergic category indiscriminately without further study of their mechanisms.

That there is a field of true allergic response to light is further suggested, though of course not completely established by the recent observations of Callaway and others^{11b, 21a} on the passive transfer of light sensitivity by the blood serum of the light-sensitive individual to normal subjects. Intradermal injection of Callaway's patient's blood serum into the skins of 3 normal individuals produced the equivalent of a Prausnitz-Küstner reaction indicative or at least suggestive of a transfer of an antibody capable of participating in a true antigen-antibody allergic reaction. The nature of the substance in the light-sensitive individual has not been identified. Large amounts of coproporphyrin I have, however, been identified in this subject's stools. No general light-sensitizing effects have been observed in the individuals who volunteered for the Prausnitz-Küstner experiment.

That light sensitiveness may be involved in an infection-allergic or infection-susceptibility complex has been suggested by the observations of Stokes and Callaway⁸³ on the general sensitizing effects of epidemic waves of intercurrent infection on dermatoses with an underlying allergic or infection-allergic complex. In addition to causing flares of processes in which a high degree of susceptibility to staphylococcus infection appeared, these authors cited 4 cases, 1 of them being the case used in Callaway's experiment, in which pyogenic or upper respiratory tract infection apparently resulted in extreme and even protracted sensitiveness to light. A physician who tolerated without reaction repeated 18-minute exposure of the palms to an S-1 lamp at 5 inches developed on the third day following an attack of epidemic bronchitis, such light sensitiveness that a 3-minute exposure to the same lamp at the same distance produced a severe burn. The importance of these considerations for the light sensitive background in lupus erythematosus and other dermatologic conditions will be again mentioned in Part II.

Systemically Acting Contributors to Photodynamic Effects. In the previous discussion a number of individual observations classifiable under this heading have been noted, but a precise definition of the mechanisms has been impossible because of inadequate present knowledge. Thus among toxic effects one might conceivably include the absorption of porphyrins developed in the metabolism of bacteria or produced at their focal sites of activity by the destructive action upon the respiratory pigment brought to them by the blood stream. Thus a group of organisms in a susceptible individual (susceptible for as yet unknown reasons) might cause a dental or an intestinal focal strain of organisms perhaps of the hemolytic type, to produce porphyrins or absorption which might, like uroporphyrin, be eliminated only or principally through the urine, or, like the coproporphyrins, through both urine and feces, with a marked preponderance *via* the feces. A mechanism of this sort is strongly suggested on purely hypothetical basis in the light-sensitization phenomena accompanying or accompanied by markedly pathogenic intestinal flora, particularly of the hemolytic

streptococcal and bacteroides types (Urbach⁸⁹). Similarly, fungi of the monilia type in the intestinal tract of pellagrins have been credited with the ability to produce photosensitizing substances. The occasional or even frequent but not invariable excess of porphyrins in the excreta of such persons is not necessarily to be regarded as more than an indicator of the precise photodynamic mechanism involved.

The influence of vitamins on photosensitizing or photodynamic mechanisms has been suggested at several points, including the possible action of vitamin C on skin pigmentation and the now well-known influence of the nicotinic acid constituent of the B complex on the behavior and elimination of porphyrins. It is not to be assumed that this interaction is necessarily direct, since as Harris³⁴ and others have pointed out, the injury to the liver which makes it unable normally to utilize ordinary amounts of nicotinic acid available in the food; the injury to the gastro-intestinal digestive mechanisms which prevent the utilization of the B complex (achlorhydria and so forth) may all participate in the relationship. Nonetheless it is clear that certain vitamins and vitamin constituents in their normal or in greatly increased amounts may be expected to influence the response of the body and particularly of the skin to light.

JOHN H. STOKES, M.D.
HERMAN BEERMAN, M.D.

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Conservation of Scholarly Journals.

The American Library Association has created a Committee on Aid to Libraries in War Areas, headed by John R. Russell, University of Rochester. The Committee hopes that American scholars and scientists will be of considerable aid in the solution of one of these problems.

The attempt to avoid a duplication of the World War difficulty in completing foreign institutional sets of American periodicals is now the concern of the Committee.

Many sets of journals, broken by the financial inability of the institutions to renew subscriptions, as far as possible will be completed from periodicals being purchased by the Committee. Many more will have been broken through mail difficulties and loss of shipments, while still other sets will have disappeared in the destruction of libraries. The size of the eventual demand is impossible to estimate, but requests received by the Committee already give evidence that it will be enormous.

With an imminent paper shortage attempts are being made to collect old periodicals for pulp. Fearing this possible reduction in the already limited supply of scholarly and scientific journals, the Committee hopes to enlist the coöperation of subscribers to this Journal in preventing the sacrifice of this type of material to the pulp demand. It is scarcely necessary to mention the appreciation of foreign institutions and scholars for this activity.

The Committee hopes that readers of this Journal will aid it in meeting these problems.

Questions concerning the project or concerning the value of particular periodicals to the project should be directed to Wayne M. Hartwell, Executive Assistant to the Committee on Aid to Libraries in War Areas, Rush Rhees Library, University of Rochester, Rochester, N. Y.

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ORIGINAL ARTICLES.

HYPERTENSION ELECTROCARDIOGRAMS EXPERIMENTALLY
PRODUCED AND ANATOMICALLY EXPLAINED.*

I. COR PULMONALE.

BY JANE SANDS ROBB, Sc.D., M.D.,
ASSOCIATE PROFESSOR OF PHARMACOLOGY,

AND

ROBERT C. ROBB, Sc.D., M.D.,
SYRACUSE, N. Y.

(From the Department of Pharmacology, College of Medicine, Syracuse University.)

A REVIEW of the subject of right heart failure, with an analysis of 210 articles concerning the causes, characteristic manifestations, and the mechanism of sudden death in clinical and experimental cor pulmonale, is now completed.^{29c} This material may be summarized briefly: Cor pulmonale may be induced by any condition raising the pressure against which the right heart must empty itself. Most authors believe that the circulatory symptoms appear only after the right heart begins to fail and that the vast majority of cases never recover from their first breakdown. Whether right heart failure is primary or secondary, as when there is occlusion of a large pulmonary area, or when reflexes cause massive pulmonary arteriolar constriction or coronary constriction, the fact remains as stated by Fineburg and Wiggers:¹⁰ "No evidence was discovered, or in our opinion has been presented by others, that circulatory failure following obstruction of the pulmonary circuit has any other cause than fatigue of the right ventricle."

Continuing the survey of cor pulmonale, we propose to discuss three additional problems: 1, the structural and functional anatomy of the right heart; 2, a review of electrocardiograms of cor pulmonale, both clinical and experimental, described in the litera-

* Aided by a grant from the Hendricks Research Fund.

ture; and 3, electrocardiograms obtained experimentally by stretching the component muscles of the right ventricle.

I. **Structural and Functional Anatomy of the Right Heart.** The cardiac dissections of MacCallum,²² Mall,²³ Tandler,³⁷ Shaner,³⁴ and others, showing that the right ventricle is mainly formed by the deep sinospiral muscle (DSS), whose fibers encircle it (parallel to the base of the heart) making both lateral and septal walls, have been repeated more recently by Robb,^{28a} Flett,¹¹ and Lowe.^{19a} The deficiency at the apex is partly filled by the superficial bulbospiral (SBS) which contributes mainly to the posterior papillary and less

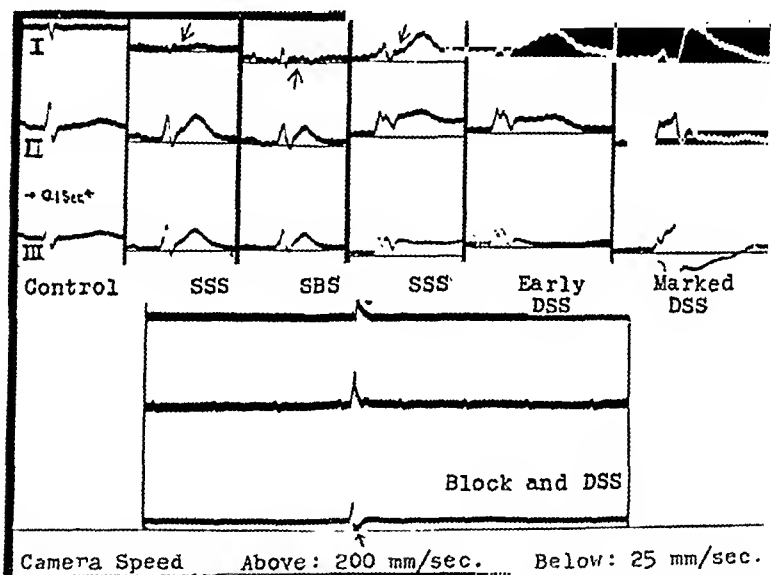


FIG. 1.—When the right ventricular pressure is gradually increased the first ECG change is slight elevation of S-T in all leads (superficial sinospiral). As the pressure increases further, S-T₁ is depressed and T₁ becomes negative, while S-T₃ is more elevated (superficial bulbospiral). The heart recovers and an SSS type recurs. Later, with beginning dilatation, S-T₁ is elevated while S-T₃ and T₃ become more negative. Finally, as death approaches, S-T₁ is greatly elevated and S-T₃ markedly depressed, also A-V block develops.

to the anterior papillary muscle (Shaner, p. 25³⁴; Robb, Fig. 1, p. 288^{28a}) and by the superficial sinospiral (SSS) which contributes mainly to the anterior and medial papillaries of the right ventricle (Shaner, p. 25³⁴; Robb, p. 68^{28a}). In previous experiments, it was shown that infarction of the two superficial muscles had no significant effect on blood pressure, whereas ligation of even a small blood-vessel supplying the deep sinospiral caused the blood pressure to fall greatly, and ligation of two or three branches to this muscle reduced the blood pressure to shock level. If a hollow organ is to "fail" or "fatigue" (Fineburg and Wiggers¹⁰), it will dilate and stretch the components of its walls, and obviously the weakest

component will fail first. The mass of the superficial sinospiral is least, hence it might be expected to fail before the others. This appears to be what happens, for many roentgenologists have reported that in right heart failure the earliest change is an increase in distance from the conus to the apex.^{29c} When the next weakest muscle, the superficial bulbospiral, stretches, the apex will be even further from the conus. When these two muscles, which support the tricuspid valve leaflets *via* the chorda tendineæ, are overstretched a tricuspid murmur should develop. Thus Moschcowitz²⁴ writes: "In long standing cases tricuspid insufficiency results." Pollock²⁷ also mentions a "systolic bruit" which he thinks was a tricuspid murmur. Finally, when the deep sinospiral is stretched beyond its optimum tension, acute failure supervenes and transverse bulging is seen.

Robb,^{28b} and Robb, Hiss and Robb³⁰ have shown that experimental acute infarction of these muscles produces a characteristic change in the electrocardiograms. Later studies apply these interpretations to human hearts with infarcts demonstrable at autopsy.^{29b} Confirmation of parts of this work has been given by Lowe,^{19a, b} who dissected the muscle bands in hearts after infarction and found that "Reconstructions of many of the scars show that they follow accurately the muscle planes and correspond to portions of one or more of the muscles which have been described." His Figure 16 presents an electrocardiogram in which S-T₁ is elevated and S-T₃ depressed, of which he writes: ". . . in specimen 28 we have a tracing indicative of an anterior wall infarction according to the description just given, whereas reconstruction of the scar shows most of the damage to be in the walls of the right ventricle, lateral and posterior as well as anterior (Fig. XVI). In this instance the tracing seems to correspond to a muscle bundle rather than to an anatomical region such as Bohning and Katz⁴ describe."

II. Electrocardiograms in Right Heart Failure. (a) Our review of electrocardiograms in cor pulmonale reveals only 14 published examples of the McGinn-White type. Let us first consider electrocardiograms in right heart failure associated with right ventricular hypertrophy in congenital hearts. Six of Abbott's¹ 7 cases we interpret as DSS muscle lesions. The seventh (Plate 13) is characteristic of an SSS lesion. All 7 of these electrocardiograms showed right axis deviation. In Schuitker's³³ data on 76 cases of right heart failure there was involvement of the SSS in 21%, of the SBS in 20%, of the DSS in 48%, and no typical muscle lesion in 11%.

Electrocardiograms labelled acute or chronic cor pulmonale are frequently seen in the literature,^{7, 9, 14, 15, 20, 21, 26, 31, 38a, b} but the uniformity of these is not as great as in those cases with a chronic rise of pressure due to congenital heart disease.

In acute cor pulmonale McGinn and White,²¹ and White^{38a, b} describe a characteristic change of the electrocardiogram, namely:

"The presence of a Q-wave and late inversion of the T-wave in Lead 3, the rather low origin of the T-wave in Lead 1, usually a distinct S in Lead 1, and an upright* T-wave (with inverted P- and QRS-waves) in Lead 4." In some instances there is definite right axis deviation. Scrutiny of their electrocardiograms shows that only the crest of the S-T₃ reaches the isoelectric level. The beginning and end of the S-T₃ are depressed below the level of the T-P interval—this is especially well shown in their Figure 5. They state that these symptoms and signs are "due in large part to dilation and partial failure of the chambers of the right side of the heart." They mention the similarity of their electrocardiograms to those "due to occlusion of the R. coronary artery, the T₃ type." Barnes³ also discusses this similarity and gives a table with points for distinguishing one from the other. Sokolow, Katz and Muscovitz³⁵ review 50 cases of cor pulmonale, classifying them according to the electrocardiogram. Their Table 1 arranges the data in four sections. Eight individuals did not survive pulmonary embolism: the electrocardiograms of 5 of these show S-T₃ depression, which is characteristic of lesions in the DSS muscle; the other 3 had SBS lesions in electrocardiograms taken from 3 to 8 days before death. Six records published are of those who survived; only 2 of these showed slightly depressed S-T₃ (Figs. 5 and 14). That 71% of those with deep sinospiral lesions died while only 43% with superficial bulbospiral lesions died, again supports the conclusion of Robb, Hiss and Robb³⁰ that lesions in the deep muscles have a graver prognosis.

Stewart, Kirk and Smith³⁶ have recently reported 12 cases of pulmonary infarction. Five of these patients died: 4 had repeated infarction before death and in the last electrocardiogram showed the DSS type of change; the fifth case seems to have died 30 hours after the first attack but the only electrocardiogram, an SBS type, was taken 13 hours before death. Here 80% of those known to show DSS lesions died (71% for Sokolow *et al.*³⁵). Of 7 patients who survived, only 2 were seriously ill and these 2 had DSS lesions, whereas the others had superficial muscle lesions. These authors claim that the changes in the electrocardiogram are essentially those described by McGinn and White,²¹ Barnes,³ Langendorf and Pick,¹⁷ Scherf and Schönbrunner,^{32a,b} and feel that the electrocardiogram is useful in differential diagnosis. They emphasize the need of repeated tracings, saying: "The changes occur in rapid succession, the electrocardiogram reverting to its more usual form more quickly than in the case of coronary occlusion."

White^{38b} (Figs. 69 and 71) shows electrocardiograms of acute and chronic cor pulmonale respectively. Both indicate a DSS lesion; they differ in that Figure 71 has a lower R₁, a deeper S₁, no Q₃, a higher R₃, and less convexity of S-T₃; they are alike in having low T₂, negative T₃, and in having slightly elevated S-T₁ and depressed

* Inverted with modern technique.

S-T₃ (the deep sinospiral type of electrocardiogram). The same type is seen in de Takats⁸ (Fig. 8) taken 8 hours after pulmonary embolism, and also in his Figures 9 and 11, as well as in Rösler's³¹ Figures 75 and 76. McCann²⁰ publishes a DSS type of electrocardiogram with the legend "record typical of that which occurs in hypertension of the pulmonary circuit."

In reviewing this extensive series of cases (not all of which were *acute* cor pulmonale), only 14 published examples of the McGinn-White type of electrocardiogram appear (McGinn and White,²¹ 5 cases; Barnes,³ Golden,¹² Knauer,¹⁴ and Scherf and Schönbrunner^{32a,b} (Case 6), each 1 case; and the 5 of Sokolow, Katz and Museovitz³⁵). It is not possible to tabulate or express as percentages the electrocardiographic variations reported in clinical papers, since sometimes the record is described but not published, S-T deviations are not always noted, the records are taken at variable times relative to the onset of symptoms and to death, seldom is a control record available to indicate any abnormality present before the pulmonary accident occurred, and finally, it is often impossible to determine whether the patient really had a cor pulmonale. Support of this opinion is contained in a personal communication from Dr. Paul D. White.*

Examples of superficial sinospiral and bulbospiral types of electrocardiograms were discovered, as were also many deep sinospiral cases. In no instance was a deep bulbospiral type (a muscle confined to the left ventricle) discovered either from published records or in descriptions of records not published. It would seem that a degree of increased pressure sufficient to cause a superficial sinospiral lesion in the right heart is not often diagnosed as due to cor pulmonale, and that among the cases diagnosed as cor pulmonale the greater proportion have deep sinospiral lesions.

(b) *Electrocardiograms from experimental work* are much more consistent. Buehbinder and Katz⁶ produced right heart failure by injection of mercury into a leg vein, whence it passed to the heart and lungs, interfering with the lesser circulation. They also clamped the pulmonary artery in some experiments. Their Figures 4, 5, 6 and 7 are predominantly deep sinospiral lesions.

Krumbhaar¹⁶ also did acute experiments during which the pulmonary artery was clamped and later released, which resulted in electrocardiograms of the deep sinospiral type. His Figure 2 of Experiment 7 shows S-T₁ elevated while S-T_{2,3} are depressed after a moderate degree of occlusion. With a greater compression of the artery, S-T was depressed in all three leads. Krumbhaar's Figure 4 (third, fourth, fifth series) shows elevation of S-T₁ and

* "It is very important to note that many cases of pulmonary embolism do not have the acute cor pulmonale—most are too slight and some are too severe (causing death in shock). Few are studied at just the right time or degree to show what I consider the typical acute cor pulmonale, hence the majority of Katz's electrocardiograms are not comparable with ours, nor are ours all of the same degree."

depression of S-T₃, which changes, up to a certain extent, were reversible. Holman and Beck¹³ in an experimental study of aortic and pulmonary stenosis publish one electrocardiogram from their Experiment 4 with pulmonary stenosis of 5 months' duration. Right axis deviation is present as is also elevation of S-T in all leads (SSS; see also their Fig. 2, Part I).

Anderson² reporting experimental work mentioned disturbance of the S-T segment. Otto²⁵ was mainly concerned with changes in the T-wave and unfortunately did not take three leads in all experiments. Crippe⁷ also did not take all three leads constantly but does write: "All showed a negative T₂ with shortened R-T interval and T starting either above or below the line." He concludes that vagal effects are unimportant and believes the changes to be asphyxial. Love, Brugler and Winslow¹⁸ report depression of all S-T segments (DSS) as a constant finding and related these changes to dilatation of the right ventricle.

III. Experimental Study of Acute Cor Pulmonale. Experiments during which the right intraeardiac pressure was gradually but progressively raised up to the point of acute failure were performed to study the apparent similarity between electrocardiograms of right-sided heart strain and muscle bundle lesions produced by ligation of specific coronary supply.

Method. Dogs and rabbits were anesthetized with appropriate doses of soluble pentobarbital, artificial respiration instituted and the thorax opened. For the study of the two ventricles 15 animals were used. Electrocardiograms (three simultaneous leads recorded either on a crystal galvanometer built by the Cambridge Instrument Company^{29a} or by three string galvanometers recording simultaneously) were taken during anesthesia, also after opening the thorax and at intervals after compression of the pulmonary artery.

Results. Considerable compression could be applied before any effect was noted. Beyond a critical point, the heart elongated from the conus to the right apex. With still greater pressure the transverse diameters of the right heart increased, the ventricle "ballooning" out. With almost complete occlusion of the pulmonary artery the left heart was firmly contracted, small and empty. Only with sudden great asphyxia did the left heart dilate after the right heart had done so. Terminal arrhythmias were uncommon. All hearts eventually slowed, even though the vagi were cut. The immediate effect on the electrocardiogram was to raise the S-T slightly in all leads above the T-P isoelectric level (+ + + * superficial sinospiral type). A second stage followed in which S-T₁ was depressed and S-T₃ further elevated (- + + superficial bulbospiral added). Still later S-T₁ elevation returned while the S-T₃ was as much depressed as the S-T₁ was elevated (+ - - deep sinospiral) (Fig. 1). The

* + or - signs refer to displacement of RS-T interval upward or downward respectively, from the T-P isoelectric level, in Leads 1, 2, 3, respectively.

occurrence and duration of these stages varied with the degree of constriction. With sudden very excessive increase of pressure, the S-T in all leads was depressed (SBS plus DSS). In no instance did a DBS type (very great elevation of S-T in all leads, characteristic of lesions in the deep bulbospiral muscle which is entirely confined to the *left* ventricle) occur in right heart failure. Right axis deviation was not observed in the acute experiments. This observation confirms that of experimental work by Buchbinder and Katz⁶ and accords with the clinical findings of Stewart *et al.*,³⁶ where in 12 cases of cor pulmonale right axis deviation was found but twice. Right heart failure, then, gives a *terminal* electrocardiogram quite different from that of left heart failure. (See Part II, p. 634, this Journal.) Moreover, this type is the one found to be characteristic of injury to the deep sinospiral muscle.

IV. **Statement of Problem for Discussion.** Our experiments indicate that in right heart failure the three component right ventricular muscles fail consecutively. This is shown by direct observation, by Roentgen ray reports as previously quoted,^{29c} and by electrocardiograms. When pulmonary pressure is increased, the distance from the pulmonary conus to the right apex (outflow tract) becomes greater. The earliest electrocardiographic changes indicate injury first to the superficial sinospiral and presently to the superficial bulbospiral muscles. It is an accepted anatomic fact that the right apex is formed by the intertwining slender portions of these two muscles. As fluid pressures within a cavity are equal in all directions, the weakest region must obviously stretch first (*i. e.*, the apex). Only when the stronger, deep sinospiral fails will the transverse diameters at the base of the right heart increase. Injury to each muscle results in a characteristic effect on the electrocardiogram. Given that the electrocardiogram will reflect previous myocardial damage, together with summation effects for each muscle acutely involved, one can explain why there are so many divergent reports of the electrocardiogram in cor pulmonale. A most important consideration is time. In acute experiments one watches the beam of light continuously, taking frequent records and thus a smooth progression showing each stage of involvement is obtained. In practice, the sicker the patient, the less is the probability of frequent and especially of terminal electrocardiograms being taken. With so many variables, it would be astonishing indeed if there were much similarity between clinical electrocardiograms.

One might mention the custom of neglecting S-T deviations of less than 1 mm. It is a fact that action currents record maximally if they pass parallel to the plane in which the electrodes are placed and record not at all if they pass at right angles to the axis of the electrodes. *Absence of large galvanometer deflections in the latter instance is no proof of tissue inactivity.* Thus when the three standard leads are recording cardiac currents, they are often oriented

so nearly at right angles to certain portions of the heart that activity in these areas fails to register (producing so-called silent areas). More recent work with chest leads has proven these are not actually "silent" areas. The minimal displacements have a significance which is generally not admitted. It would be equally amateurish either to diagnose and to make a serious prognosis from every minor deviation of S-T (less than 1 mm.) or to neglect such minor deviations for analysis and localization. Bourne and Evans⁵ found that 17% of 80 anginal patients showed electrocardiographic evidence in Lead IV only and they concluded that "Lead IV helped to emphasize the importance of *slight* changes in Leads I, II and III . . ."

Summary and Conclusions. 1. Electrocardiograms taken in experimental right heart failure agree in form with those of previous authors.

2. Whatever the cause, pulmonary hypertension, if immediately great, may produce acute right heart dilatation, or if sufficiently prolonged, results in right heart hypertrophy and eventually in failure.

3. The essential mechanism of failure consists in the progressive stretching of the three component muscles of the right ventricle. The weakest area at the right apex is formed by the superficial sino-spiral muscle and strain of this muscle is heralded by some elevation of RS-T in all leads. A second weak area, the superficial bulbo-spiral portion of the apex becomes involved and this is recognized by further elevation of RS-T in Leads 2 and 3 and coincident depression of S-T in Lead 1. Widening at the base indicates failure of the deep sino-spiral and is evidenced by marked depression of RS-T in Leads 2 and 3, and either elevation or depression of RS-T in Lead 1, depending on the degree of concomitant superficial bulbo-spiral involvement.

4. It is immaterial whether the exciting cause of muscle failure is rise of pressure within the right heart or whether failure is secondary to asphyxia produced either directly or reflexly. When these muscles are under tension and unduly stretched the same electrocardiographic picture is produced as if the muscle were infarcted or otherwise damaged.

5. Because these muscles fail consecutively and because damage to each has its own effect on the electrocardiogram, and especially because there may have been preëxisting disease (or effects due to drug action), a valid explanation is available for the great variation in clinical electrocardiograms during an attack of cor pulmonale.

6. In these experiments, with the chest open, a dilated right heart was not associated with right axis deviation.

7. The McGinn-White type of electrocardiogram is probably associated with a moderately severe degree of rise of intracardiac pressure, stretching all three of the component muscles. When intracardiac pressure is dangerously increased, all S-T intervals are

depressed in addition to some one or all of the changes described by McGinn and White, Barnes, or Rösler.

8. If intracardiac pressure increases slowly and not too greatly, the electrocardiogram may be wholly unaffected, or if the pressure increases are rapid and extreme, any combination of muscle injury pictures may occur, thus accounting for the variable reports concerning electrocardiograms in pulmonary embolism and hypertension.

9. The employment of muscle bundle localization may serve to increase the value of electrocardiograms in the recognition, treatment and prognosis of cor pulmonale.

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HYPERTENSION ELECTROCARDIOGRAMS EXPERIMENTALLY PRODUCED AND ANATOMICALLY EXPLAINED.*

II. LEFT VENTRICULAR STRAIN.†

BY JANE SANDS ROBB, Sc.D., M.D.,
 ASSOCIATE PROFESSOR OF PHARMACOLOGY,

AND

ROBERT C. ROBB, Sc.D., M.D.,
 SYRACUSE, N. Y.

(From the Department of Pharmacology, College of Medicine, Syracuse University.)

It is well known that the electrocardiogram is frequently altered in systemic hypertension. Shift of the apparent electrical axis to the left, displacement of the S-T segment (generally downward in Lead 1 and upward in Lead 3), negativity of T_1 and positivity of T_3 are regarded as characteristic. No explanation for such signs has been substantiated. Current teaching is summarized by Best and Taylor⁴ (p. 303) who describe these changes in the electrocardiogram associated with hypertension and offer three theories in explanation:

"(1) That it is due to the *greater mass of muscle*, the electrical changes occurring in the hypertrophied chamber overbalancing those of the normal side. This theory has been rendered untenable by the discovery that the electrocardiographic features which were thought to be produced by one ventricle are actually produced by the other (p. 312). In other words, the electrical changes in the *sound* ventricle overbalance those of the hypertrophied side." Master⁹ apparently adheres to this hypothesis, believing the electrical signs are gradual developments due to the increasing size of the left ventricle. In his own series of 152 patients with hypertension, 117 (74%) presented left axis deviation. He emphasizes that changes were gradual and depended "on the duration of the hypertension and the degree of enlargement of the left ventricle and not on changes in the heart muscle" (p. 91). He also writes (p. 92): "The changed anatomical configuration of the muscle masses may alter the time of onset of regression of the electrical excitation wave in specific tissues like the bundle branches or in the myocardium itself and thus may produce characteristic electrocardiograms in the

* Aided by a grant from the Hendricks Research Fund.

† Strain is defined as: A forcible stretching, tending to alter shape, an injury to a muscle due to excessive tension or use.

standard leads." On page 94, he mentions that "the duration of the QRS complex is normal and there is neither notching or slurring which often occurs in myocardial involvement" and again on page 100, "However, the widened, slurred and notched QRS complex and the large initial negative deflection in lead IV (deep Q4) indicate involvement of the myocardium."

"(2) *Altered position of the heart.* The greater mass of the hypertrophied ventricle causing rotation of the heart around its longitudinal axis; this probably plays only a minor rôle.

"(3) *Slowed conduction* over the bundle branch supplying the hypertrophied ventricle as a result simply of the lengthening of the conduction pathway incident to the enlargement of the ventricular cavity, or to actual injury of the conducting tissue associated in some way with the cardiac disease. According to Barker¹ and associates, one or other of these factors is the most probable explanation of the characters of the electrocardiogram in ventricular hypertrophy."

Barnes and Whitten² agree with Barker *et al.* in supporting this third hypothesis predicated ventricular "strain."

According to Pardee¹¹ (p. 14), the QRS is inscribed "while the contraction is spreading throughout the ventricular muscle" (excitation). In Macleod's⁷ "Physiology" (p. 284) one reads: "The electrical changes generated within this bundle (His) are not detectable in the E.C.G. but the gradual spread of activity through the powerful ventricular muscle, which is thereby induced, gives rise to the complex series of waves comprising the QRS group."

Resnick,^{12a} studying the effect of anoxemia in A-V conduction, found that conduction was first stimulated and then slowed. The effect of anoxemia on conduction varied with severity, duration, the general condition of the animal, its heart rate, and was thought to be due to a "direct effect on the muscle." In another paper^{12b} on the effect of anoxia on intraventricular conduction, he found that at first the QRS interval shortened but later lengthened. He concludes that "ventricular aberration in clinical cases is an indication of more or less serious disturbance of the function of the Purkinje tissues."

Bazett and Sands³ commonly found an increased QRS in dogs with experimental aortic regurgitation.

All these observations tend to show that where the intraventricular pressure is increased (as it is mechanically in aortic regurgitation), or where there is a concomitant anoxemia (which may occur when the intraventricular pressure is considerably raised), there is slowing of intraventricular conduction. (This widening of QRS was regularly obtained in animal experiments.)

Experimental Study. *Methods.* Left heart strain was produced according to a method previously employed by Wiggers¹⁶ (see also Katz, Ralli and Cheer,⁵ and Otto¹⁰). Young dogs or rabbits were put on artificial

respiration and subjected to ligation of several arteries within the thorax (both carotids, the innominate, the left subclavian, and the descending thoracic aorta). In two series of experiments 15 animals were used. Blood pressure was recorded from one carotid through a mercury manometer. The pressure in this small arterial system was still further increased by injecting saline or glucose through the side arm of the recording cannula, thus increasing the pressure against which the heart must empty. The chest incision was not sewed up but after each inspection the parts were drawn together and the animal covered with a blanket to prevent undue cooling of the heart's surface.

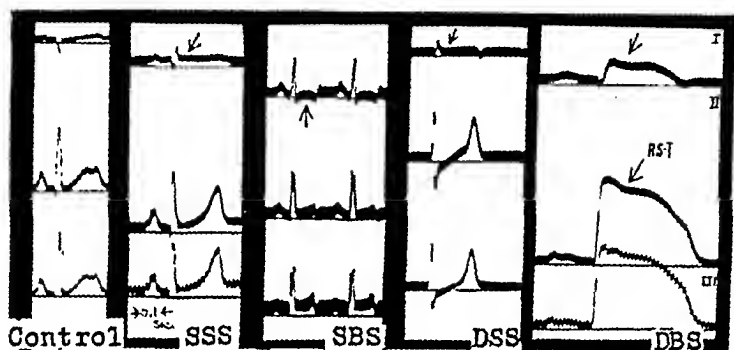


FIG. 1.—Types of muscle bundle lesions sequentially associated with progressive left ventricular strain. Paper speed 50 mm. per second. Standardization: 1 cm. = 1 mv. SSS = superficial sinospiral type of tracing (RS-T = + + +). SBS = superficial bulbospiral type (RS-T = - + +). DSS = deep sinospiral type (RS-T = + - -). DBS = deep bulbospiral, a terminal lesion (RS-T = + +, + +, + +).

Results. It was found that the amplitude (especially of R in Lead I) increased as soon as the pressure was raised by tying the descending aorta (no veins were tied). The earliest physical change noted was a tendency for the heart to become longer and narrower (pericardium closed). With continuing moderately high pressure or with sudden increase of pressure, the S-T segment in all leads of the electrocardiogram was slightly elevated. This is the characteristic change found in experimental infarction of the superficial sinospiral muscle (see Fig. 1, SSS). When pressures were raised still higher, the amplitude of the pulse pressure increased, and presently S-T₁ became depressed, and S-T₃ became elevated. This is the characteristic change found in experimental infarction of the superficial bulbospiral muscle (see Fig. 1, SBS). If fluid was rapidly introduced into the arteries and an electrocardiogram taken during the forceful injection, it was noted that T₂ abruptly became negative and that this negativity disappeared and T₂ became as positive as ever when the heart had adjusted to the pressure increase. This T₂ reversal could be carried out many times during an experiment, but eventually the negativity of T₂ tended to become permanent. In one experiment fluid was introduced into the ventricle itself, 80 cc. given very rapidly. The left ventricle dilated and fibrillation resulted (see Fig. 2).

Such experiments indicate the following order of strength of left ventricular muscles, weakest superficial sinospiral, then superficial bulbospiral, deep sinospiral and finally the deep bulbospiral as the strongest. This order one would expect from the relative muscle masses. The cuff (deep bulbospiral) is, of course, not absolutely the heaviest, but it is the thickest and experimentally the most essential to the maintenance of blood pressure.

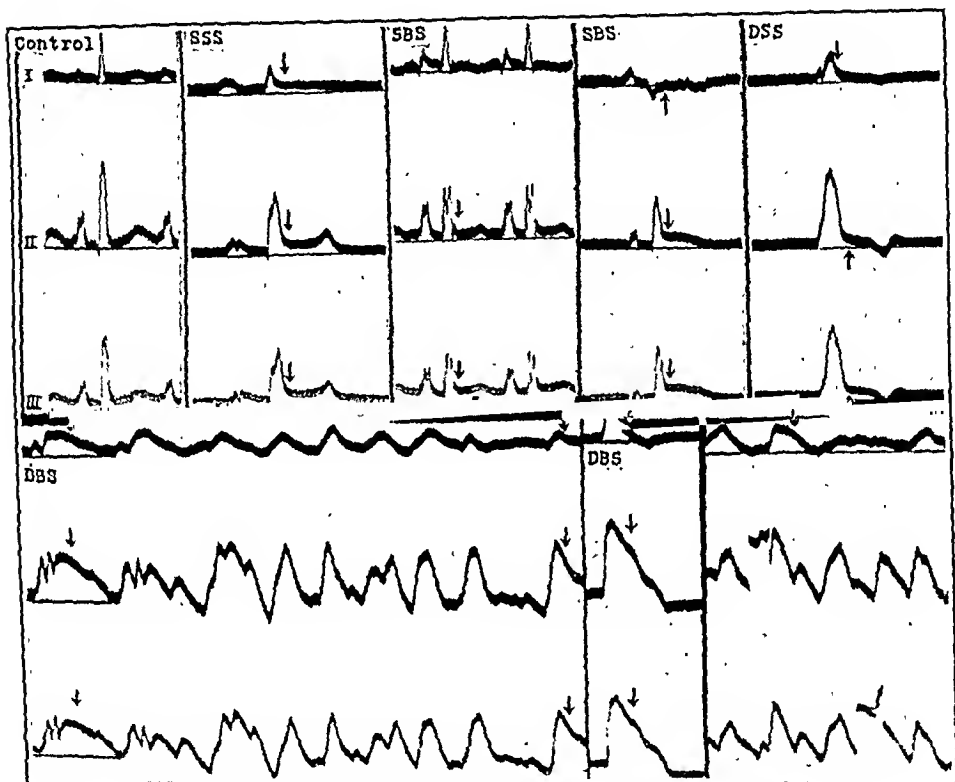


FIG. 2.—Standardization and symbols as in Figure 1. Following gradual rise of intracardiac pressure sufficient to involve three muscles, during recording of first DBS segment, rapid pressure rise was instituted. Note the development of fibrillation followed by spontaneous recovery to a DBS type of record. A second rapid increase of pressure produced another fibrillation from which there was no recovery.

As pressure of a fluid in a closed cavity is exerted equally in all directions, the internal pressure would be expected to dilate first the weakest part of the left ventricle, the apex, which is enclosed by the thin interlocking portions of the superficial sinospiral and bulbospiral muscles only. Not until pressures were greater would the thicker deep sinospiral and deep bulbospiral muscles dilate, expanding the diameters at the base of the heart.

Previous studies (Mall,⁸ MacCallum,⁶ Robb and Robb¹³) have shown that under certain conditions there is differential hypertrophy of various ventricular muscles. Presumably the weaker muscles, if under continued strain, would stretch or dilate sooner than the stronger muscles. Such stretching of the superficial sinospiral and

bulbospiral muscles offers an explanation of the common and well-established observation (made both clinically and experimentally) that the outflow tract increases in length previous to expansion of the left ventricle at the base and agrees with Uhlenbruck's¹⁵ statement regarding "enlargement" at the apex (which does not necessarily mean hypertrophy), as the cause of electrocardiographic changes in hypertension.

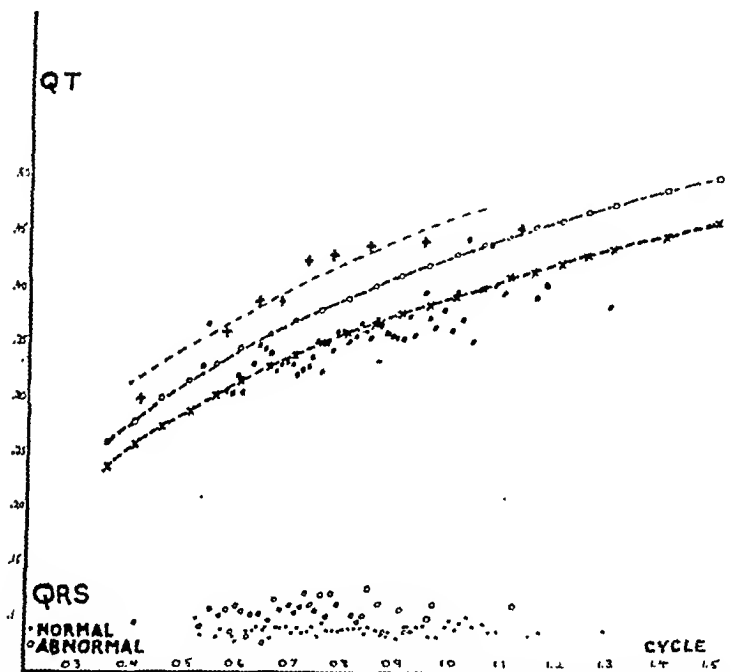


FIG. 3.—Duration of Q-T and QRS plotted against duration of cycle in seconds. Q-T is prolonged in the hypertensives partly due to a longer QRS and partly due to a longer S-T. Q-T: x-x Ashman and Hull's averages for normals; o-o Ashman and Hull's upper limit of normal values; + average data for 100 ambulatory hypertensive patients; large dots, average Q-T durations in 300 medical students from this laboratory. QRS: small dots, QRS duration in the same 300 medical students; o, average QRS durations in 100 ambulatory hypertensive patients.

In brief, it is demonstrated that the intraventricular pressure can be increased and by gradual increase, strain can be put successively upon the various muscles causing one after another to fatigue. The blood was at all times bright red and did not appear to be deficient in O_2 content. Possibly the alteration in conduction is related to the increased length of conduction pathways (Best and Taylor) occasioned by the tendency of the ventricle to dilate, the effect being to slow conduction along certain pathways and alter the total algebraic summation of all electrical activity.

Clinical Observations. Recently 100 ambulatory hypertensive patients (from Hypertension Clinic of Dr. B. Levinson) have been studied.

Figure 3 presents Q-T and QRS duration plotted against cycle length in these patients. One sees that Q-T duration is definitely increased over that of normals. The values range from 0.3 second when the cycle length is 0.4 second, up to a duration of 0.45 when the cycle length is 1.13 second. QRS duration is also increased in many instances.

S-T changes, when present in clinical hypertension, are comparable to those obtained in acute animal experiments. There were 16 among the 100 whose S-T intervals were isoelectric (16%). Of this group, 75 (75%) showed signs of only superficial muscle strain. There were 37 (37%) who showed a slight elevation of S-T in all leads (superficial sinospiral type of muscle injury) and 38 (38%) others presented depressed S-T₁ and elevated S-T₃, the superficial bulbospiral type of record. Only 9 showed even a mild degree of deep sinospiral alteration (R-T₁ elevated, R-T₃ depressed), which scarcity (9%) is to be expected since none of these patients were decompensated. None showed the deep bulbospiral type of electrocardiogram (maximal elevation of R-T in all leads) which again supports our previous observation that patients with a lesion in this muscle will not be ambulatory and tend to die quickly. Marked deep sinospiral or deep bulbospiral lesions would be expected only during decompensation and immediately before death, hence to see such pictures we require more records taken of patients in extremis.

Discussion. 1. Granting that the electrocardiogram characteristic of hypertension does occur in patients having hypertension and large hearts, it likewise occurs in those with small hearts (also noted by Master,⁹ p. 106). Since electrocardiographic signs of hypertension may appear without cardiac enlargement, *size* meaning generalized hypertrophy cannot be the exclusive cause of such signs.

One sees similar electrocardiograms (usually either superficial sinospiral or superficial bulbospiral types) produced under various conditions placing extra demand on the left ventricle, such as aortic stenosis and insufficiency, coarctation of aorta with hypertension, von Gierke's disease, and patent ductus arteriosus with large left ventricle (see Master's Figs. 31 A and I, 38, 52, 55, 57, respectively). The superficial muscle type is sometimes found in pericarditis where generally the superficial muscles alone are involved (see Master's Fig. 61). When both right and left hearts are enlarged, it is obvious that any muscle type or an admixture of all types could be present (see Master's Figs. 47, 48, 49, 51, 54).

2. Uhlenbruck¹⁵ has suggested that "hypertrophy of the apex" may be the explanation of these electrocardiographic changes. It is certainly true that the outflow tract becomes lengthened early and also the apex tends to become rounded. Injury or "strain" in this region may be a more convincing explanation of electrocardiographic signs. Further evidence concerning this change at the apex is found in an experimental study of aortic regurgitation by

Bazett and Sands.³ When the aortic cusps were broken, and thus an acute rise in left intraventricular pressure produced, the heart silhouette at once became longer and narrower. In that article Figures 2 and 5 show anterior-posterior and lateral Roentgen rays before and after the operation. Their Figure 7 shows electrocardiograms taken before operation, at 6 weeks after the first operation, and at 11 months after the first and 9 months after the second operation. At 6 weeks, one finds S-T₁ elevated, T₁ negative, T₂ negative, T₃ diphase, S-T_{2,3} depressed. In the subsequent record, S-T₁ is still elevated, T₁ is flattened, T₂ is diphase, S-T₃ is still depressed, T₃ is positive. There is no left axis deviation. Thus in a chronic experiment where a mechanical load raising the left intraventricular pressure is allowed to operate for 11 months, a deep sinospiral type of electrocardiogram is obtained. Presumably less regurgitation might have resulted in a superficial sinospiral or a superficial bulbospiral lesion and more in a deep bulbospiral, but with three valves injured at two operations a deep sinospiral type did appear. Schnitker¹⁴ reports 8 cases having coarction of the aorta; half of these showed a deep sinospiral type of tracing.

3. Increased intraventricular pressure not only stretches the component muscle bands of the ventricular wall but also would elongate the conducting pathways (whatever histologic forms these may prove to have. Best and Taylor,⁴ as previously quoted, mention simple lengthening of a conduction pathway as a possible explanation of the electrocardiographic change. This elongation may be the mechanism of the increase in QRS duration noted in patients and experimental animals alike where intraventricular pressure is increased (Fig. 3).

Conclusions. 1. Because in acute experiments on young animals no hypertrophy and myocardial damage (in the sense of infarct or connective tissue replacement) is present, one must attribute the various results to change in size of the ventricles dependent upon "strain," that is, increased intraventricular pressure with dilatation (rather than hypertrophy).

2. Such a stretching of the musculature demonstrably alters conduction even to the point of causing ventricular fibrillation.

3. Either development of an injury current within a single muscle band or differential slowing of conduction (including recovery) may be regarded as the essential factor resulting in the characteristic electrocardiograms.

4. These S-T shifts in the electrocardiogram, caused by putting strain upon the individual muscle bundles, are the same as those produced by experimental infarction of the same muscle bundles.

5. Acute centralized systemic hypertension, experimentally induced, initiates a series of electrocardiographic changes reflecting the severity of the disturbance. The left ventricle is enclosed by four muscle masses which give way in sequence: the superficial

sinospiral first, the superficial bulbospiral next, later the deep sinospiral muscle, and in extremis, the deep bulbospiral muscle. Our clinical experience parallels the animal data.

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STUDIES ON THE DISTRIBUTION OF POTENTIAL CONCERNED IN THE FORMATION OF ELECTROCARDIOGRAMS.

BY CHARLES C. WOLFERTH, M.D.,

PROFESSOR OF CLINICAL MEDICINE, SCHOOL OF MEDICINE, UNIVERSITY
OF PENNSYLVANIA,

MARY MILLER LIVEZEY, M.D.,

FELLOW OF THE ROBINETTE FOUNDATION, SCHOOL OF MEDICINE, UNIVERSITY
OF PENNSYLVANIA,

AND

FRANCIS CLARK WOOD, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA, PA.

(From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the
University of Pennsylvania.)

DURING the past 2 years we have been attempting to study various relations among peripheral differences of electrical potential created by cardiac activity in normals and also in patients with various types of cardiac abnormality.¹² This work has led to the development of concepts which we have been unable to reconcile with the time-honored views of Einthoven² regarding the distribution of potential on the body surface. Our observations indicate that

certain definite patterns of variations with time, of differences of potential can be recognized over considerable areas of the body surface by the use of appropriate methods. Some of these patterns obtained between paired areas near the heart undergo decrement as distance of paired areas from the heart increases, but along certain radial lines extending from the heart little alteration in contour of pattern is demonstrable between paired areas. It would seem therefore that the distribution of potential on the body surface from electrical phenomena in the heart is quite different from what Einthoven conceived it to be when he made the series of unverified assumptions which underlie the equilateral triangle hypothesis.

It is remarkable that, as judged from the literature, the equilateral triangle hypothesis receives almost universal acceptance without question as to the validity of the assumptions which underlie it. Gildemeister's⁴ demonstration of the electrical properties of tissues, Eyster, Maresh and Krasno's⁵ studies of impedance, and Katz's⁶ studies of the effects of altering conduction from certain parts of the heart, none of which has been controverted, all seem to be ignored and the superstructure erected upon Einthoven's assumptions grows more and more elaborate.

We have previously shown that differences in potential of ventricular origin between areas in the region about the root of the left arm are, with certain exceptions, much greater than those between corresponding areas on the right side.¹² We proposed that, in the majority of subjects, ventricular potential variations in the left arm are principally, but not entirely responsible for the ventricular pattern of Lead 1.* Furthermore, with certain exceptions, the ventricular contour of Lead 1 was found to resemble that of CR₅, although the amplitude of deflections in the chest lead was usually much greater than in Lead 1. In some cases, the resemblance may be closer between Lead 1 and a CR Lead made to some position in the neighborhood of C₅ (*i. e.*, C₄, C₆ or a position slightly above and to the left of C₅) than between Lead 1 and CR₅ itself. If one moves the chest electrode from C₅ to positions successively nearer the left arm, the deflections diminish in amplitude, although the pattern remains much the same.

These observations, based on studies of approximately 700 cases, suggested that potential variations in the left arm are derived mainly from electrical phenomena in those parts of the ventricles responsible for potential variations in the neighborhood of the C₅ position.

Since these observations were published we have made further studies. It has been found that if an electrode connected with the right arm lead wire is placed on the tip of the right acromial process and an electrode connected with the left arm lead wire is placed at

* This statement does not apply to the auricular waves: in this paper we discuss ventricular effects only.

various positions along a line from the tip of the right shoulder to the C_1 position (the arm being regarded as an electrically intermediate position between the tip of the shoulder and the axilla), the ventricular complexes all show the same general pattern as that of

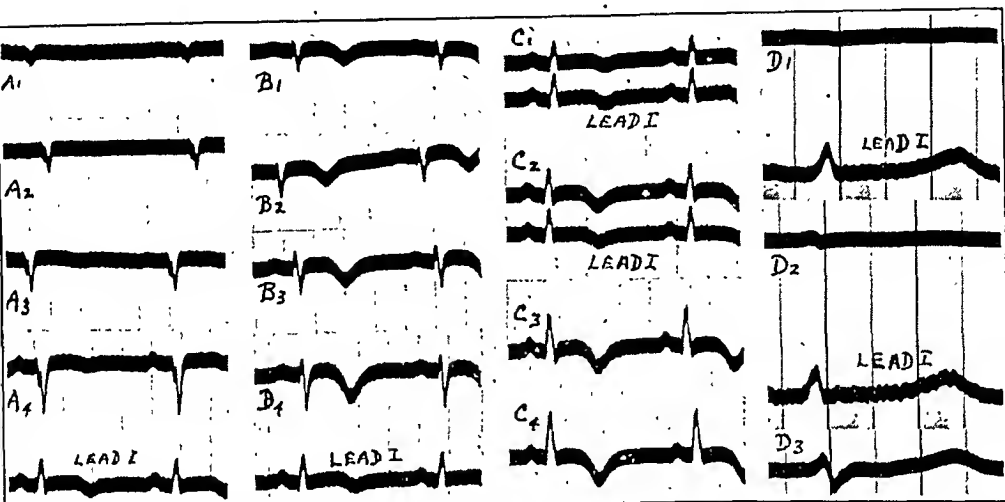


FIG. 1.—In tracings A_1 , A_2 , A_3 , and A_4 the right arm electrode was placed on the tip of the right acromial process. In A_1 the left arm electrode was placed in the right axilla, in A_2 on the right chest just external to the pectoralis muscle, in A_3 approximately half way between the root of the arm and the C_1 position and in A_4 on the C_1 position. Note the similarity in contour of the ventricular complexes and increase in size of deflections as the C_1 position is approached.

In tracings B_1 , B_2 , B_3 , and B_4 the right arm electrode was on the tip of the left acromial process. In B_1 the left arm electrode was placed in the left axilla, in B_2 on the left chest just external to the pectoralis muscle, in B_3 approximately half way between the root of the arm and the C_5 position and in B_4 on the C_5 position. Note the similarity in contour of the ventricular complexes and increase in size of deflections as the C_5 position is approached. The pattern, however, is quite different from that of the right side.

C_1 , C_2 , C_3 , and C_4 are tracings obtained by pairing various areas of the A and B series, using the same polarity as in Lead 1. In C_1 the right and left shoulders were paired, in C_2 the right and left axillae, in C_3 areas intermediate between the roots of the arms and chest positions, and in C_4 the chest positions C_1 and C_5 were paired. Note the similarity of all these tracings to Lead 1. In some cases, as is pointed out in the text, the close similarity in contour cannot be maintained except by pairing areas at somewhat different levels.

Tracings D_1 , D_2 , and D_3 were obtained from a different patient. In D_1 (made simultaneously with Lead 1) the electrodes were attached and the connections made as is shown in Figure 2, A. The balance of potential on the right side in accordance with the relationship, $P_b - \frac{(P_a + P_c)}{2} \doteq 0$, is shown. In D_2 a similar balance of potentials on the left side is shown. In D_3 the "a" and "c" areas on the left side are paired.

Film speeds in A , B , and C , 25 mm. per second; in D , 75 mm. per second.

CR_1 (Fig. 1, A_1 , A_2 , A_3 and A_4), the deflections becoming successively larger as the left arm electrode is moved to positions successively near the C_1 position (sometimes even as near the ventricles as the C_2 position). A similar study on the left side along a line from the tip of the left shoulder to the C_5 position with the upper and lower

electrodes similarly connected yields tracings similar in pattern to each other (although far different from those obtained from the right side) with gradual increase in amplitude of deflections as the C_5 position is approached (Fig. 1, B_1 , B_2 , B_3 and B_4). However, in order to obtain the best correlation on the left side, one may have to place the electrodes along a line to the C_4 or C_6 position, the direction probably depending on the size of the heart and its relation to the chest wall. Furthermore, in many cases the correlation on the left side does not hold to an area quite so near the heart as one of these C positions but stops somewhat above and to the left of C_5 .

After having performed the above experiments and having ascertained the most favorable line to follow on the left side, and the level to which the correlation holds, a series of tracings closely resembling Lead 1 (except for size of deflections) can be made by pairing various areas along the right-sided line (right arm electrode) with appropriate areas along the left-sided line (left arm electrode). In order to obtain the closest correlation with Lead 1, it may be necessary to pair areas at different levels on the two sides, the positions being found by the method of trial and error. The electrode on the left must often be placed higher than the one on the right. The deflections tend to grow larger as the electrodes are moved to paired areas nearer the C_1 and C_5 positions (Fig. 1, C_1 , C_2 , C_3 and C_4).

The above studies suggested to us that the changes in potential of ventricular origin in the right arm are derived mainly from electrical phenomena whose sites are in the same parts of the heart as those responsible for the potential changes of the C_1 position, just as the previous studies had suggested that the potential changes of the left arm are derived from electrical phenomena in the same parts of the heart responsible for the potential changes of the C_5 position or some neighboring area. Furthermore, there appeared to be marked decrement in potential variation between the C_1 position and the right shoulder and between the C_5 position and the left shoulder.

If the distribution of potential variations along a line from C_1 to the right shoulder tip and from C_5 to the left shoulder tip (the arm being electrically intermediate between the axilla and shoulder tip) is what we have described it to be, it should be possible to find three positions along either of these lines—"a", a point nearest the C_1 or C_5 position; "c", a point furthest from the C_1 or C_5 position; and "b", a point intermediate between "a" and "c", which would be so related to one another that the difference in potential between area "b", on the one hand, and the mean of the potentials of "a" and "c" on the other, would approximately equal zero for all instants of the ventricular cycle. If we represent potential variation of cardiac origin at any instant of ventricular activity by the letter P, and designate the areas by subscripts, this relationship can be expressed in the following form which can be tested galvanometrically:

$$P_b - \frac{P_a + P_c}{2} \doteq 0$$

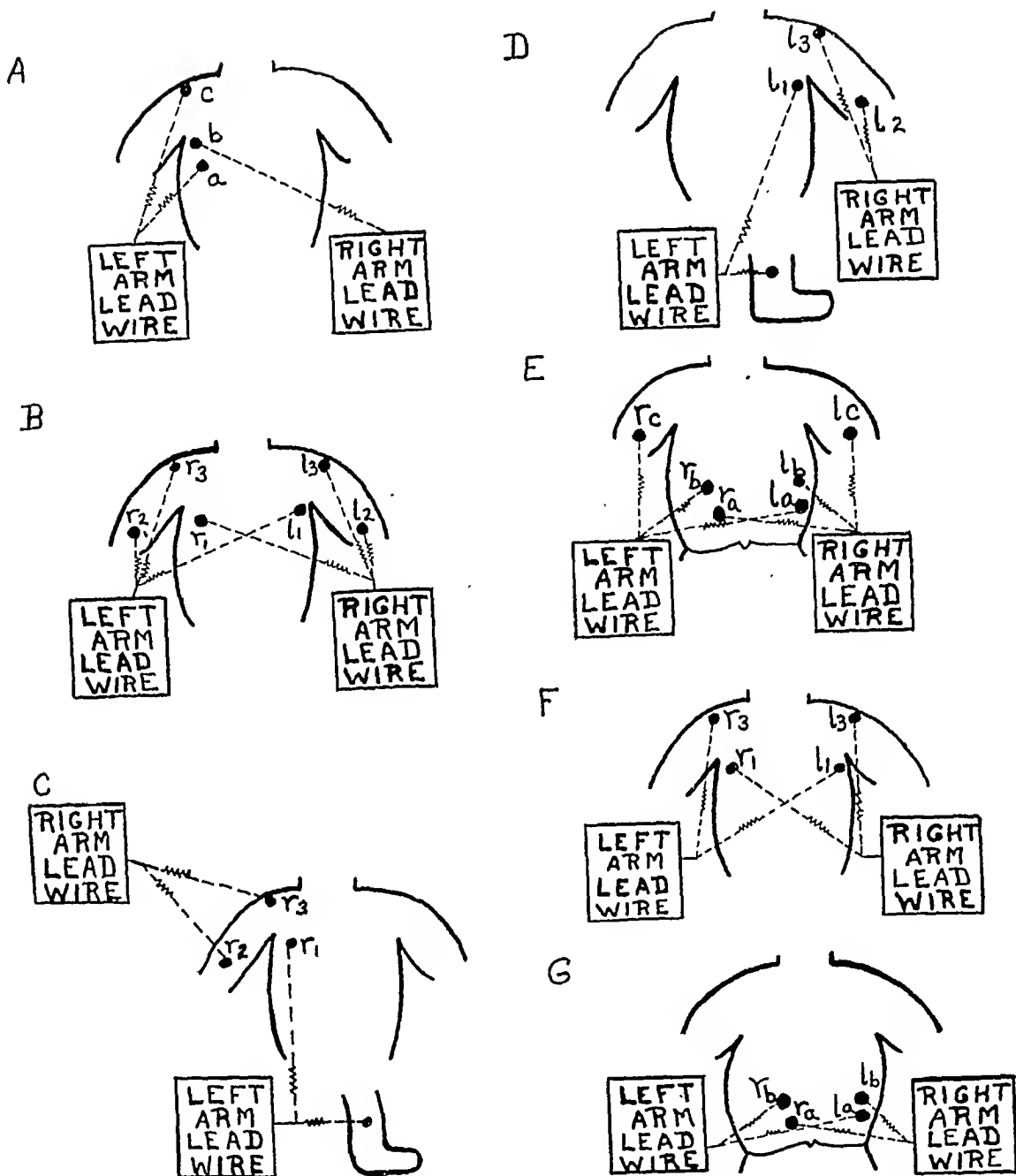


FIG. 2.—A, Position of application of electrodes and connections to demonstrate the relationship, $P_b - \frac{(P_a + P_c)}{2} \doteq 0$ (see Fig. 1, D_1 and D_2). B, Approximate positions of electrodes and connections used in the test of Equation 4. The r_1 and l_1 positions are found by exploration (see Fig. 3, B_1). C, Approximate positions of electrodes and connections used in Equation 6 (see Fig. 3, B_2). D, Approximate position of electrodes and connections used in Equation 7 (see Fig. 3, B_3). E, Approximate position of electrodes and connections used in the test of Equation 4 in which the C_1 and C_2 positions are included. The r_b and l_b positions are found by exploration (Fig. 3, C_1). F, Electrode positions and connections used to reproduce Lead 1 as shown in Equation 8 from positions at some distance from the heart (Fig. 3, B_4). G, Electrode positions and connections used to reproduce Lead 1 (Fig. 3, C_4). This relationship is shown by the Equation, $(P'_{la} + P'_{rb}) - (P'_{ra} + P'_{lb}) = P'_{lc} - P'_{rc}$, which is derived from Equation 4 after substituting the subscripts a, b and c, for 1, 2 and 3 respectively (the principle is the same as that of Equation 8 (Fig. 2, F) but in this case the electrode positions are much nearer to the heart.)

Various combinations of positions can be used to show this relationship on either side. Thus on the right side, the tip of the acromial process may be designated area "c", an anterior axillary position area "b", and a position halfway to C, tentative area "a". Electrodes are placed on each of these areas and the one on area "b" connected with the right arm lead wire of the electrocardiograph. The wires to electrodes on positions "a" and "c" are interconnected after the interposition of 50,000 ohms resistance* in each, and connected with the left arm lead wire (Fig. 2, A). If the lead taken according to these arrangements shows ventricular deflection of any magnitude, the tentative "a" position is not the proper one to satisfy the relationship and this electrode is moved either upward or downward along the line until the smallest possible deflections are obtained. An "a" position can be found in which these are usually less than 1 mm. for the QRS complex (Fig. 1, D₁ and D₂).

Such a result furnishes experimental confirmation for the statement previously made regarding the similarity of patterns of differences of potential along these lines. In dealing with such intricate patterns as QRS complexes it would seem out of the question to assume that the differences of potential could be balanced in this way merely by coincidence. We therefore feel justified in stating that the patterns of differences of potential remain remarkably constant along each of these more or less radial lines from precordium to shoulder tips (although quite different on the two sides), but that decrement in potential variation seems to be considerable as distance from the heart increases. As a matter of fact, it is these characteristics which make possible the balancing of potential differences by this simple procedure.

The above-mentioned relationships offer a new approach to the study of electrocardiography, *i. e.*, by the development of a method for isolating certain patterns of ventricular potential variation which are present on the body surface. We shall assume that potentials of non-cardiac origin can be ignored with safety in electrocardiography. Our standard of reference for variations of potential of cardiac origin is an arbitrarily assumed base line of potential, upon which the cardiac potential is superimposed. It is not essential that this assumed base line of potential be identical for various paired areas, since differences which may be present are neutralized in the process of electrocardiography. It is obviously impossible to measure directly variations of potential of cardiac origin against this arbitrarily assumed constant potential.

The term P which we have used in the relationship

$$P_b - \frac{P_a + P_c}{2} \doteq 0,$$

* An amplifier type electrocardiograph must be used when these high resistances are employed and the room must be shielded from alternating currents.

to designate ventricular potential may be considered to be composed of two possible components with reference to this arbitrarily assumed constant potential. One of these is that part of the potential variation of areas along the radial lines mentioned which is responsible for the pattern of differences of potential recorded between various paired areas situated along each of the lines. This component of the potential which is balanced experimentally may be designated by the term P' with a subscript to represent the area. However, in addition to this P' pattern, there is a theoretical possibility of additional potential change in all the areas, which however unlike the P' pattern is not subject to decrement and is therefore the same in all the areas under consideration. Such potential may be designated "X". The relationship

$$P_b - \frac{P_a + P_c}{2} \doteq 0$$

may therefore be expressed as follows:

$$(P'_b + X) - \frac{(P'_a + X) + (P'_c + X)}{2} \doteq 0 \quad \text{or} \quad P'_b - \frac{P'_a + P'_c}{2} \doteq 0$$

It is obvious from the above that the actual value of the "X" potential does not influence the accuracy of the approximation

$$P'_b - \frac{P'_a + P'_c}{2} \doteq 0,$$

since "X" has the same value at any instant in each of the 3 areas.

However, in certain of the relationships to be discussed later in this paper the actual value of the "X" potential, if it exists, becomes a matter of importance. As will be shown by experimental data, there are a number of indications which suggest that it is non-existent. We shall therefore assume provisionally for purposes of clarifying the discussion, that it can be ignored but shall later consider its possible bearing on results.

If three areas could be found with patterns of ventricular potential variation so related that at every instant the potential variation of one area equalled the sum of the potential variations of the other two, one could utilize this relationship to measure the potential variations of a fourth area. Thus, if we represent the ventricular potential for any instant by P' (as defined above) and if Areas 1, 2 and 3 fulfilled the relationships expressed above, this could be stated:

$$P'_1 = P'_2 + P'_3 \quad \text{or} \quad P'_1 - P'_2 - P'_3 = 0 \quad \text{or} \quad P'_1 - (P'_2 + P'_3) = 0$$

If then we wish to measure the potential variations of the left leg or any other area, we add this expression to both sides of the third equation without changing the equality.

Thus:

$$\{P'_1 + P_{\text{left leg}}\} - \{P'_2 + P'_3\} = P_{\text{left leg}}$$

The value for the left side of this equation can be determined galvanometrically if the locations of Positions 1, 2 and 3 are known, and

since, according to the assumption, the values balance each other at every instant of time except for $P_{\text{left leg}}$, the galvanometer can be made to record the potential variations of the left leg as indicated by the equation.

The attempt to put the above principle into practice led to certain difficulties. Obviously the relationship $P'_1 = P'_2 + P'_3$ cannot be tested galvanometrically, so that one still lacks a method for finding areas with such relationships even if they do exist. However, if two such combinations of areas could be discovered, one on the right and the other on the left, a galvanometric test of balance of cardiac potential variations could be made, although such a test would establish only the correctness of the combined equation and not that of each component part.

Our studies of the peripheral electrical field mentioned above have shown that combinations of three areas can be found, along either of the lines from the right or left chest position to the corresponding shoulder tip, whose relations are such that there is practically no difference of potential between one and the *mean potential* of the other two. We therefore attempted to find combinations of three positions along each line whose relationship is such that the potential variations of one area equals the *sum* of the potential variations of the other two. If, on the right and left sides we designate the three hypothetical positions r_1, r_2, r_3 and l_1, l_2, l_3 respectively, r_1 and l_1 being nearest the heart, r_3 and l_3 farthest away and r_2 and l_2 the intermediate positions, the assumed relationships of their potential of ventricular origin for any instant of time may be expressed as follows:

$$(1) \quad P'_{r_1} - (P'_{r_2} + P'_{r_3}) = 0$$

$$(2) \quad P'_{l_1} - (P'_{l_2} + P'_{l_3}) = 0$$

If Equation 1 be subtracted from Equation 2 one obtains

$$(3) \quad [P'_{l_1} - (P'_{l_2} + P'_{l_3})] - [P'_{r_1} - (P'_{r_2} + P'_{r_3})] = 0$$

By rearrangement of terms

$$(4) \quad [P'_{l_1} + P'_{r_2} + P'_{r_3}] - [P'_{r_1} + P'_{l_2} + P'_{l_3}] = 0$$

In formulating the simple equations stated above we have had to make the assumption not only that the "X" potential is negligible, but that the decrement in ventricular potential in the areas under discussion is such that, as distance from the heart increases, variations of ventricular potential from the arbitrarily assumed base line at the distal end of either line must not be more than half those at the proximal end. Therefore in our first test of Equation 4 it seemed best to choose r_3, r_2, l_3 and l_2 positions far from the heart. Consequently, electrodes were attached to the tips of each shoulder (r_3 and l_3 positions) and to each arm (r_2 and l_2 positions). The attempt was then made to find r_1 and l_1 positions which in conjunction with these other four arbitrarily selected areas would satisfy Equations

tion 4. A tentative r_1 position is chosen on the chest wall about half way between the attachment of the right arm and the C_1 position, tentative l_1 about half way between the attachment of the left arm and the C_5 position and electrodes are fixed to these two areas. Wires from the electrodes on the three areas designated in the first bracket of Equation 4, after the interposition of 50,000 ohms resistance in each, are interconnected with the left arm lead wire of the galvanometer. Similar connections of the three areas designated in the second bracket of Equation 4 are made with the right arm lead wire (Fig. 2, B). The sensitivity of the galvanometer is standardized so that 1 m.v. = 2 cm.* If difference of potential is found to exist between the two groups of areas (*i. e.*, if there is an appreciable string deflection during ventricular systole), Equation 4 is not satisfied. The next step, then, is to find by the process of trial and error the r_1 and l_1 positions which most nearly satisfy the equation. This is done by exploring on the right side until an area is found which yields the smallest deflections with the electrocardiographic connections described above. This area now becomes tentative r_1 and is used in the next procedure which is to explore the left side until an area is found which yields the smallest possible deflections. This area is now designated l_1 . The right side is then reexplored for minor corrections in r_1 position which best satisfy Equation 4 (Fig. 3, B₁).

We have used the above procedure in 23 cases and have been able to balance the potential variations so that with the sensitivity mentioned above, deflections did not exceed 1 mm. at any time during the QRS complex. Ordinary chest electrodes 2.9 cm. in diameter were used. It is possible that if we had used smaller electrodes an even better experimental approximation to the prediction would have been obtained. The r_1 and l_1 positions which yielded the best results for the QRS complexes were not always the identical r_1 and l_1 positions which yielded the best results for the T waves, possibly because of differences in position of the ventricles during these two phases of systole. Having found combinations of areas whose potential variations of ventricular origin balance each other in such a way as to satisfy Equation 4 with a close approximation to accuracy, it is implicit in the results that Equation 3 must also be satisfied. This can be shown in the following way: The ventricular potential of an additional area such as that of the left leg may be added to each bracket without altering the value of the equation. Thus:

$$(5) [(P_{\text{left leg}} + P'_{l_1}) - (P'_{l_1} + P'_{l_2})] - [(P_{\text{left leg}} + P'_{r_1}) - (P'_{r_1} + P'_{r_2})] = 0$$

The values for each of these brackets can be obtained galvanometrically. Thus, in the case of the first bracket, electrodes are

* The electrocardiogram resulting from this standardization requires a correction by the factor 1.5. The standardization of 1 m.v. = 3 cm. was not used for technical reasons.

applied on the designated areas and each connected with a wire in which 50,000 ohms resistance is interposed. Beyond the resistances, the wires to electrode positions designated in the first parenthesis are interconnected with the left arm lead wire. Those in the second parenthesis, after the interposition in each of 50,000 ohms of resistance, are similarly interconnected with the right arm lead wire. The galvanometer is carefully standardized so that 1 m.v. = 2 cm. and a tracing made (Fig. 2, *D*). A similar procedure is then carried out in the case of the positions designated in the second bracket (Fig. 2, *C*). In all cases in which Equation 4 had been satisfied, the patterns of ventricular deflections obtained by these two procedures are with one exception* quite similar (Fig. 3, *B*₂ and *B*₃).

LEGEND FOR FIG. 3.

FIG. 3.—Tracings obtained from a patient several days after the development of acute posterior infarction. In the left column conventional leads are shown made with a film speed of 25 mm. per second. *B*₁ represents the balance of potentials obtained by the method of Equation 4 using positions far from the heart (see Fig. 2, *B*, for diagram of connections). *C*₁ represents the balance of potentials obtained by the method of Equation 4 including positions near the heart (see Fig. 2, *E*). *B*₂ represents the "left leg potential" obtained by the method of Equation 4 (see Fig. 2, *C*). *B*₃ represents the "left leg potential" obtained by the method of Equation 7 (Fig. 2, *D*). *C*₂ represents the "left leg potential" obtained by the method of Equation 6, using positions near the heart as shown in Figure 2, *E* (in this instance, the *C*₁ position is used as one of the areas for balancing the *C*₂ pattern of potential). *C*₃ represents the "left leg potential" obtained by the method of Equation 7, using positions near the heart as shown in Figure 2, *E* (in this instance a position slightly above the *C*₁ position is used as one of the areas for balancing the "*C*₃ pattern" of potential). *B*₄ is the tracing obtained using the areas and connections indicated by the left side of Equation 8 (Fig. 2, *F*) taken simultaneously with a tracing made according to the connections indicated in the right side of Equation 8 (which is Lead I). *C*₄ is the tracing obtained using the areas and connections indicated in the left side of the equation stated in the legend of Figure 2, *G*, taken simultaneously with a tracing made according to the connections indicated in the right side of that equation (which is Lead I). *B*₅ represents $r_1 - r_2$ (Fig. 2, *F*). *C*₅ represents $r_a - r_b$ (Fig. 2, *G*). *B*₆ represents $l_1 - l_2$ (Fig. 2, *F*). *C*₆ represents $l_a - l_b$ (Fig. 2, *G*). *B*₇ represents "right arm potential" obtained by the method of Equation 6, using positions distant from the heart (but analogous to method shown in Figure 2, *C*). *C*₇ represents "right arm potential" obtained by the method of Equation 6 in which the *C*₁ position was one of the areas used (i. e., from positions near the heart). *B*₈ represents "left arm potential" obtained by the method of Equation 6, using positions distant from the heart. *C*₈ represents "left arm potential" obtained by the method of Equation 6 in which the *C*₁ position was one of the areas used.

According to the relationships stated in the text, *B*₅, *B*₇, *C*₅ and *C*₇ should be practically identical. All show very small deflections. However, very slight discrepancy or technical error may distort the pattern when the deflections are small as in the case of *C*₅ and to a lesser extent *C*₇. *B*₂, *B*₃, *C*₂ and *C*₃ should be identical. In this group the pattern is well maintained because of larger deflections, despite the differences in the procedures by which the tracings were obtained. *B*₄ and *C*₄ should be practically identical and *B*₆, *B*₈, *C*₆ and *C*₈ should also be practically identical. The patterns are well maintained in both groups; the discrepancies in size of deflections could have been corrected by slight readjustments in positions of electrodes.

* When the deflections obtained by these procedures are extremely small the combination of technical error (which may be considerable in any one of a long series of experiments, each rather complex) plus admitted slight discrepancy between theory and experimental findings, is sometimes great enough so that similarity of pattern cannot be demonstrated. (See Fig. 3, *B*₅ and *C*₅, *B*₇ and *C*₇.) Such discrepancies are to be expected in dealing with areas of very slight potential variation.

It is obvious from these relationships that Equations 1 and 2 are approximately correct and the "X" potential negligible or each contains a similar error due to similar values of "X" potential in each. If they are correct, the two galvanometric procedures just described actually record the potential variations of the left leg.

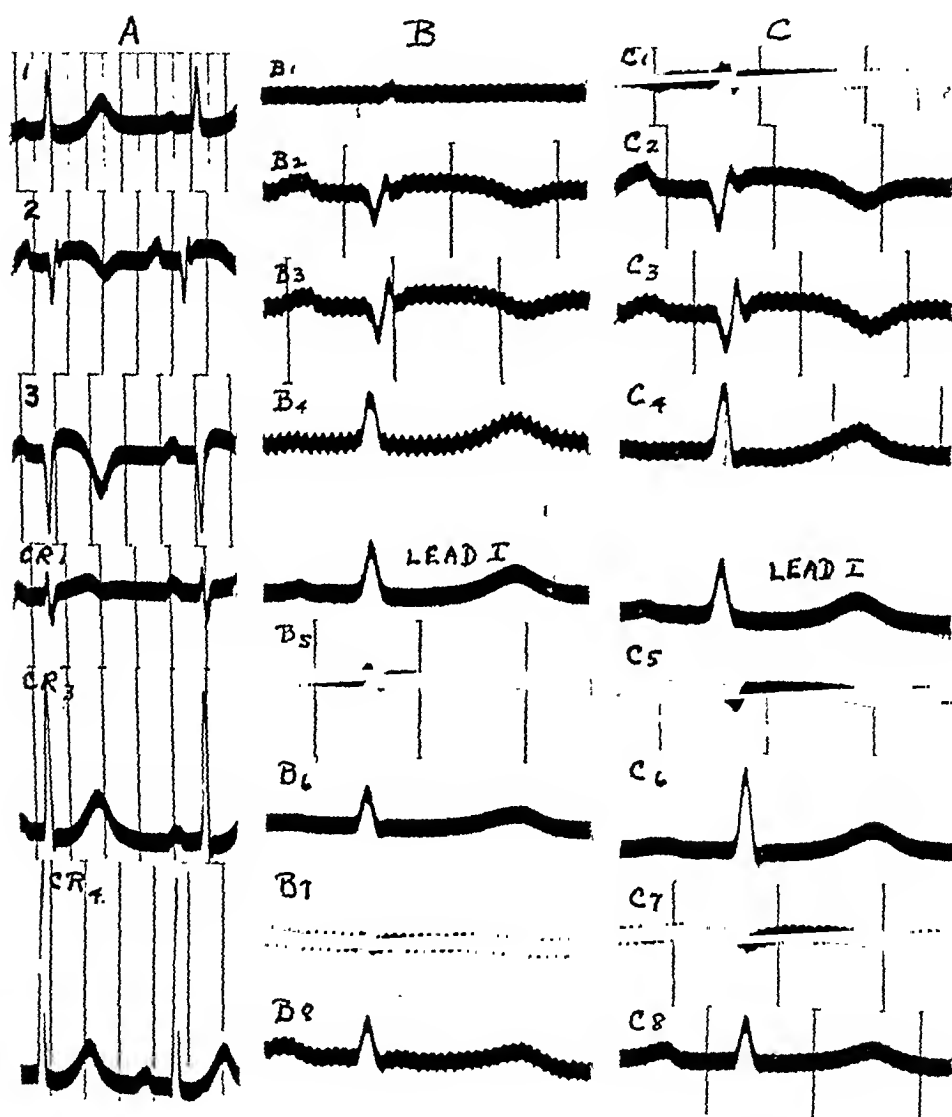


FIG. 3

This can be shown mathematically by adding $P_{\text{left leg}}$ to both sides of Equations 1 and 2. Thus:

$$(6) \quad (P_{\text{left leg}} + P'_{r1}) - (P'_{r1} + P'_{r2}) = P_{\text{left leg}}$$

and

$$(7) \quad (P_{\text{left leg}} + P'_{l1}) - (P'_{l1} + P'_{l2}) = P_{\text{left leg}}$$

Another relationship implicit in the satisfaction of Equation 4 is shown by transposition of terms. Thus from Equation 4 the following is derived:

$$(8) \quad (P'_{l1} + P'_{r1}) - (P'_{r1} + P'_{r2}) = P'_{l1} - P'_{r2}$$

The value of $P'_{l_1} - P'_{r_1}$ is obviously that of Lead 1, since the l_1 area is the left arm and the r_1 area is the right arm. This relationship can be tested by taking an electrocardiogram after disconnecting the right and left arm electrodes from the connections used in the test of Equation 4 (Fig. 2, *F*). It is found that, despite the fact that none of the four electrodes indicated in the left side of Equation 8 is on either arm, the result obtained is practically identical with Lead 1 (Fig. 3, *B*₄).

From Equation 8 the following is obtained by rearrangement of terms:

$$(9) \quad (P'_{l_1} - P'_{l_2}) - (P'_{r_1} - P'_{r_2}) = (P'_{l_1} - P'_{r_1}).$$

Equation 9 can be tested by recording the differences of potential of the areas in each parenthesis on the left side of the equation simultaneously with Lead 1 (areas but not connections shown in Fig. 2, *F*). If Equations 1 and 2 are correct, $P'_{l_1} - P'_{l_2}$ (Fig. 3, *B*₆) must represent the ventricular potential variations of the left arm and $P'_{r_1} - P'_{r_2}$ (Fig. 3, *B*₅) must represent the ventricular potential variations of the right arm. Practically identical patterns of potential variation are also obtained for the right arm and for the left arm by the use of the procedures indicated in Equations 6 and 7 (Fig. 3, *B*₇ and *B*₈).

These studies obviously add further evidence to support the view expressed earlier in the paper concerning the formation of the traditional Lead 1 of the electrocardiogram irrespective of the value of "X" potential. Thus Lead 1 is formed by: (1) the pattern of potential variation of a chest position just outside the C_5 position which has undergone great decrement at a position so far away electrically from the heart as the left arm, minus (2) the pattern of potential variation of the C_1 position which has also undergone great decrement at a position so far away electrically from the heart as the right arm. However, the results of our former study showed that usually (although not always) it is the potential pattern of the left arm which dominates Lead 1.¹²

Our studies, however, have not proven that the "X" potential is negligible nor that we have succeeded in recording the ventricular potential variations of a single area. It is conceivable that a pattern of potential common to all six of the areas r_1 , r_2 , r_3 , l_1 , l_2 and l_3 may be present, which is not subject to the decrement of the C_1 and C_5 patterns of potential and is therefore not recognized. If this were the case such a pattern could not be recognized by the procedures used in this study and would therefore introduce a constant error in our attempts to measure the potential variations of a single area. Thus, it might be argued that when we utilize Equations 6 and 7 to measure the potential variations of the left leg, we may have balanced out of the equation the potential variations of the type subject to decrement in the "r" positions and in the "l" positions, but not the "X" potential variation. The latter would have to be transmitted from electrical charges in some part of the heart in con-

tact with a good conductor such as muscle, so that no important differences in this pattern of potential would exist among any of the six areas. If this were the case, a part (or possibly most) of the potential variation which we ascribe to the leg would actually be derived from the upper part of the body.*

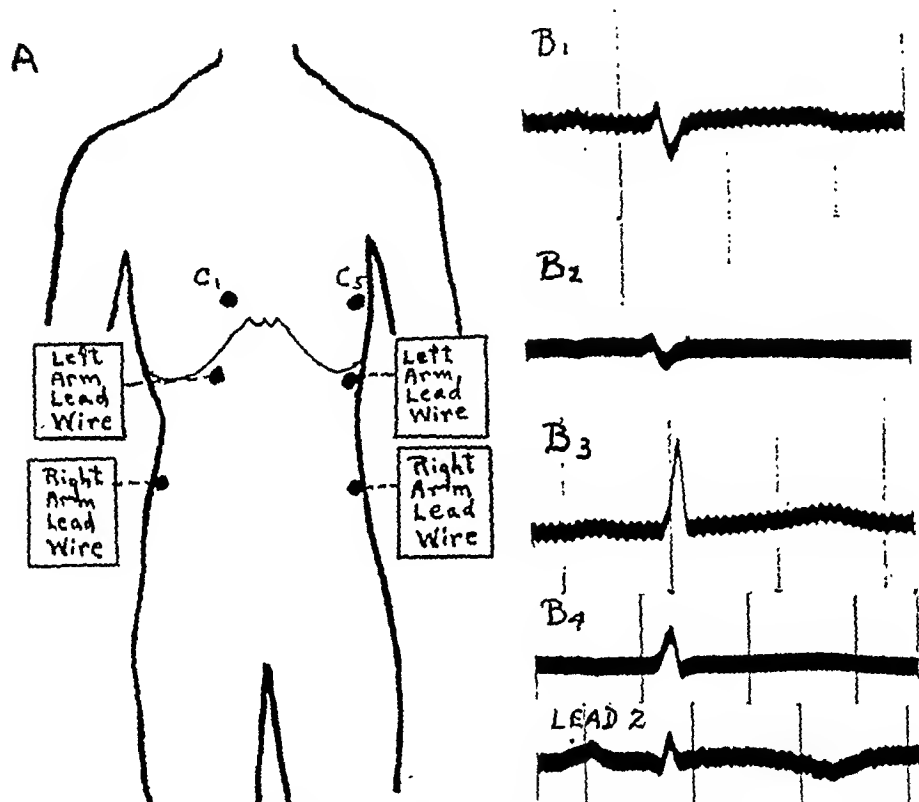


FIG. 4.—A shows positions of application of electrodes on abdomen to show the presence of the C_1 and C_5 patterns of potential below the level of the diaphragm. B_1 shows the C_1 pattern of potential recorded by the method of Equation 6. B_2 is obtained by pairing the areas on the right side of the abdomen as shown in Diagram A. Note the resemblance of ventricular patterns. B_3 is the C_5 pattern of potential obtained by the method of Equation 6. B_4 was obtained by pairing the areas on the left side of the abdomen as shown in Diagram A. Note the resemblance of ventricular patterns except for a small S wave in B_4 . (Film speed in all tracings 75 mm. per second.)

Some preliminary studies of the part of the electrical field below the diaphragm have convinced us that the distribution of at least three different patterns of potential variation can be recognized in that part of the body. For such a demonstration a patient is selected who presents the typical electrocardiogram of posterior infarction so that leads from each upper extremity to parts of the body below the diaphragm present certain identifiable common characteristics. If a tracing is made with the left arm lead wire

* If "X" potential is not ignored, Equation 6 must be written as follows:

$$(P_{\text{left leg}} + P'_{r1} + X) - (P'_{r1} + X + P'_{r1} + X) = P_{\text{left leg}} - X$$

electrode on the upper abdomen below the C_1 position and the right arm lead wire electrode on the lower part of the right flank, a tracing can be obtained in which the deflections are very small but in which the similarity in contour to those obtained along the line from C_1 to the top of the right shoulder can be recognized (Fig. 4, A , B_1 and B_2). This seems to mean that the C_1 pattern of potential is rather feebly distributed over the right side of the abdomen with decrement as distance from the heart increases. If a similar lead is made from the left upper abdomen below the C_5 position to the left flank, the similarity in contour to the leads made along the line from C_5 to the top of the left shoulder can also be recognized (Fig. 4, A , B_3 and B_4). This appears to mean that the C_5 pattern of potential is also rather feebly distributed down the left side of the abdomen with decrement as distance from the heart increases. These phenomena, however, are apt to be overlooked in tracings between the right arm and various lower parts of the body, even in cases with posterior infarction, since the pattern is dominated by the potential variations presumably derived from the area of injury and subject to little decrement on the body surface below the diaphragm (Fig. 4, Lead 2).

In view of the apparent variability in decrement of the various component units which make up the potential variations of areas in the lower part of the body, we attempted to test Equation 4 by including positions as near to the heart as possible, in order to obtain information as to whether this state of affairs might exist in the upper part of the body. Our previous findings indicated that it should be possible to satisfy Equation 4, using such positions, provided decrement in potential variation between the chest and arm positions on each side is sufficiently great. Furthermore, if Equation 4 could be satisfied using positions, some of which are near the heart, and if identical results could be obtained in Equations 6 and 7, we should have to conclude that either Equations 1 and 2 are correct, or the "X" potential variation, not reflected in the previous studies (because it was identical at the six positions previously used), is also present and of the same size at areas so near the heart as the C_1 and C_5 positions. In order to avoid confusion in terminology when using areas near the heart, the three areas on the right side are designated r_a , r_b and r_c , and the three areas on the left side, l_a , l_b and l_c , r_a and l_a being the areas nearest the heart, r_b and l_b the intermediate areas, and r_c and l_c the areas furthest from the heart. Thus, in the series of equations which have been formulated r_a and l_a can be substituted for r_1 and l_1 ; r_b and l_b for r_2 and l_2 ; and r_c and l_c for r_3 and l_3 respectively. Electrodes were placed on the arms (in this instance areas r_c and l_c), on the C_1 and C_5 positions (in this instance areas r_a and l_a) and on intermediate positions between the attachments of the arms and the C positions (tentative areas r_b and l_b). The method used was that described previously

except that the intermediately placed electrodes were used to explore (Fig. 2, *E*). The approximate satisfaction of Equation 4 is technically much more difficult when these positions are used than when all the electrodes are placed a considerable distance away from the heart. The sources of difficulty we have encountered have been as follows: On the right side, difficulties all seem to have to do with decrement in potential variations between the C_1 position and the right arm. Thus, in many cases, the potential variations of the right arm seem to be practically negligible and under these circumstances the r_b position is found to be so close to the r_a (C_1) position that the electrodes could not be placed on these two positions without touching each other. In others, potential variations of the right arm may be greater than half those of the C_1 position so that no intermediate point will satisfy the equation. Under these circumstances, the equation can occasionally be satisfied by moving the electrode from an intermediate position to the top of the right shoulder. On the left side, similar difficulties may be encountered because of rate of decrement in potential variations, but in addition, the direction of the line extending downward and inward from the shoulder, along which electrodes can be placed to satisfy the equation, becomes a matter of importance. This line usually extends down to a position just outside the cardiac apex. Occasionally the equation cannot be satisfied by having the l_a position at the level of C_5 but can be satisfied by placing it a few centimeters higher. Another source of difficulty is the relatively great potential variation at positions so near the heart, so that moving an electrode only a few millimeters may make considerable difference in results. However, even with all these difficulties, a reasonably close approximation to Equation 4 can be obtained by using positions near the heart as well as by using positions further from the heart.

Having satisfied Equation 4, with positions near the heart (Fig. 3, C_1), the various other procedures mentioned previously, which are implicit in this relationship, can be carried out with similar results. Thus, after finding the areas which satisfy Equation 4 (Fig. 2, *E*), we obtain, by disconnecting the electrodes attached to the arms (Fig. 2, *G*), a tracing resembling Lead 1 (Fig. 3, C_4) despite the fact that the four positions used in making the tracing may be quite distant from either arm, and at least 2 of them very close to the heart.

The results of the procedures indicated by Equations 6 and 7 for the determination of "potential variations of a single area" are found to be practically the same when the above combinations of areas are used, as in the case of combinations of areas all of which were further away from the heart (Fig. 3, C_2 and C_3). Since in this test the arms are designated areas r_c and l_c , we rearrange terms of Equation 9 (using the appropriate subscripts for this combination of areas) thus:

$$(10) \quad (P'_{la} - P'_{lb}) - (P'_{ra} - P'_{rb}) = P'_{lc} - P'_{rc}$$

In this instance $P'_{lc} - P'_{rc}$ represents the difference in potential between the left and right arms, *i. e.*, Lead 1. The value of $P'_{lc} - P'_{lb}$ (Figs. 2, *G*, and 3, *C₆*) is found galvanometrically to be similar to that of $P'_{lb} - P'_{lb}$ (Figs. 2, *F*, and 3, *B₆*) of Equation 9 despite the marked differences in position of the areas. Likewise $P'_{ra} - P'_{rb}$ (Figs. 2, *G*, and 3, *C₅*) is found to be similar to $P'_{ra} - P'_{ra}$ (Figs. 2, *F*, and 3, *B₅*).*

Discussion. The demonstration, (1) that certain patterns of ventricular potential variation are present throughout certain body surface areas located along more or less radial lines from the precordium to the shoulder tip, (2) that they are subject to decrement as distance from the heart increases, thus permitting a balance of the potential variations of one position within a given area (with approximate accuracy) against those of two other positions within the same area, and 3, that there are certain other phenomena which depend on these relationships, indicates the advisability of reexamining prevailing concepts regarding the distribution of potential of cardiac origin on the body surface.

In a system so complex as the human body, composed of many different tissues (membranes, muscle sheets and muscle bundles, bone, fat, lungs, digestive tract and skin), with their different electrical properties, it would seem difficult to justify continued adherence to simplifying assumptions which ignore this state of affairs. A sounder course of procedure would have been an attempt to establish the possible limits of error of such assumptions. If they are as untenable as our experimental work suggests, the subject of cardiac potential distribution at body surface areas some distance from the heart requires reinvestigation.

When electrograms are made with one electrode directly on heart muscle or separated from it only by the thin layer of epicardium, the fundamentally important work of Lewis^{7,8} indicates that the major wave of negativity, or the so-called intrinsic deflection of the QRS complex, is due to the arrival of the excitatory process in the subepicardial muscle directly under the electrode. The pre-intrinsic deflection which is positive is derived, according to Lewis, from some deep lying mass of muscle tissue. Lewis showed that the pre-intrinsic deflections begin all over the ventricular surface at nearly the same time, and that the time at which they are recorded over the right ventricle is not disturbed even after transection of the right bundle branch (although the arrival of the intrinsic deflection is delayed by this procedure). He concluded therefore that pre-intrinsic deflections recorded from an electrode over the right ventricle may represent the passage of an excitation wave through portions of the left ventricle. Furthermore, Lewis' experiments showed that, when the positive pre-intrinsic deflections were recorded at the epicardium, negativity was present in an electrode placed on

* Such discrepancies as are present are due chiefly to technical errors.

the endocardium. Wilson¹⁰ who has also performed experiments bearing on this subject has found, in agreement with Lewis' endocardial leads, that the potential of the ventricular cavity with reference to any area distant from the heart falls at the beginning of the QRS complex. Thus it would appear to be clearly established that negativity in deeper layers of the myocardium with reference to the potential of a point distant from the heart may occur at the same time as positivity of the epicardium with reference to the same point. This phenomenon, which is undoubtedly one of major importance in electrocardiography, for which various explanations have been proposed which need not concern us here, is an indication of the complexity of the problem of potential distribution.

When the electrode is moved from the heart to the chest wall directly overlying the heart, the factors determining potential variation have somewhat different relative importance despite the fact that, when the heart muscle is healthy, the QRS pattern resembles that of the epicardial electrogram with pre-intrinsic, intrinsic and post-intrinsic deflections, and the T wave remains upright. In the first place, electrical activity of any kind within the heart may be expected to produce much less effect on the chest walls than on the epicardium. In the second place, it is probable that the effect upon the epicardial electrode is that produced in a small volume of the heart near the electrode. The potential difference between a precordial electrode and some other (skin) electrode is on the other hand most probably determined by electrical phenomena in a volume of the heart considerably larger than that which contributes most to the corresponding potential difference for an epicardial electrode. Thus, when two chest leads are made from positions directly over the ventricle, it seems useful to assume that the potential difference between them is determined in large part by electrical phenomena within certain volumes of the heart. The effect of a particular small volume of the heart upon the difference of potential between the electrodes will depend upon many factors: A, The areas of the skin covered by the electrodes. B, The distances of the particular volume from the electrodes. C, The orientation of muscle fibers in which the phenomena arise, with respect to the electrodes. D, The electrical properties of the intervening tissues.

Everyone who has had experience with multiple chest leads knows that change in the pattern may occur as the exploring chest electrode is moved from one position to another near by. Furthermore, when a lesion is present in the anterior wall of the left ventricle and is reflected by a pathologic pattern of potential variation, maximum at a certain area on the precordium, the pattern in adjacent areas is probably also influenced by the lesion. However, at some distance from the precordial region of maximum abnormality, the electrical effects derived from a part of the ventricle with a normal

architecture may so overshadow the effects from the abnormal region that the pattern of potential variation becomes of the normal type. This does not necessarily mean that no effect is being registered from the area of the lesion, but merely that the effect is not great enough to produce a pathologic pattern.

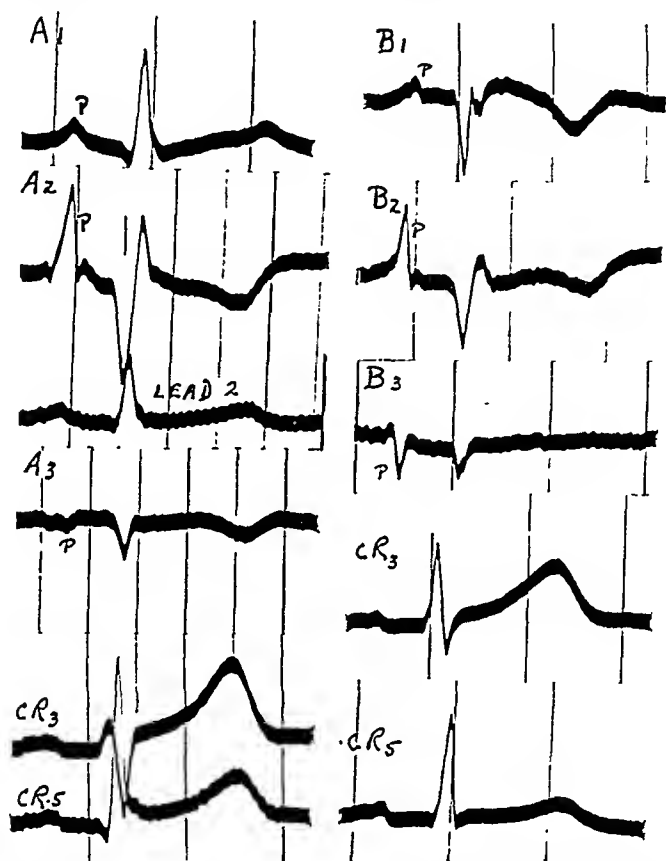


FIG. 5.—The tracings in the left column were obtained from a presumably normal control. A_1 , A_2 and A_3 are esophageal leads in which the esophageal electrode is connected with the left arm lead wire and paired with the right arm electrode on the right arm. In A_1 the esophageal electrode was below the auricular level. Note the similarity of the ventricular deflections to those of Leads 2 and CR_5 . In A_2 the esophageal electrode was pulled upward about 3 cm. to the auricular level. Note the large P wave and the reversal of ventricular pattern to the so-called endocardial type. In A_3 the electrode has been pulled upward about 3 cm. above the auricular level.

The tracings in the right column were obtained from a patient in the healed stage of posterior infarction. B_1 , B_2 and B_3 were made with the esophageal electrode in positions similar to those of A_1 , A_2 and A_3 , respectively. Note that there is a marked difference in ventricular pattern from that of the healthy heart below the auricular level but not at the auricular level. (Film speed, 75 mm. per second.)

The normal pattern of potential variation in the lower esophagus seems to be much like that recorded from the anterior chest wall (Fig. 5, A_1 and CR_5). However, as the esophageal electrode is

moved gradually upward there may be a startling reversal of pattern with an initial large wave of negativity in the QRS complex and an inverted T wave (Fig. 5, A_2), much like the pattern found anteriorly over an area of infarction. In view of the type of endocardial pattern found by Lewis^{7,8} one might raise the question, as Brown¹ has done, whether an electrode lying in the neighborhood of the auricles (or even higher in the esophagus) may not tap the endocardial potential more than that of the epicardium. The importance of this esophageal pattern on the ventricular potential of various body surface areas cannot be evaluated at this time but it might be considerable in certain areas.

While there is a constantly changing contour in the pattern of potential variation as an exploring chest electrode is moved from one position to another directly over the ventricles, the contour over certain other parts of the chest, as has been demonstrated in this paper, does not change materially. Thus from chest positions not directly overlying the ventricles but not far away, patterns of potential variation are obtained on each side, which as we have shown, remain practically constant (subject only to decrement as distance from the heart increases) along radial lines extending as far away from the heart as the tip of each shoulder. We have no satisfactory explanation for these observations. Obviously the body is not functioning with reference to these areas as a homogeneous fluid conductor surrounding the heart. One is reminded of the interesting suggestion of Eyster, Maresh and Krasno³ that certain tissues (possibly in this case the lungs) may function as "leaky electrostatic condensers" for certain parts of the heart in close relationship with them.

Since our studies have shown that Lead 1 represents the result of subtracting the C_1 pattern of potential (derived chiefly from one part of the heart), from the C_5 pattern* (derived chiefly from another part of the heart) after each has undergone the decrement between its C position and the corresponding arm, the rather dubious scientific standing of Lead 1 becomes apparent. The possible advantages of studying separately the C_1 and C_5 patterns rather than Lead 1 are obvious. Adherents to Einthoven's views must necessarily think that Lead 1 is extremely important. However, since we have shown that the potential patterns which are subtracted from one another to produce Lead 1 are derived mainly from different parts of the heart, it would appear that the contour of the deflections of Lead 1 should have less significance than those of the C_1 and C_5 patterns considered separately. Another objection to Lead 1 is the fact that its contour is affected by certain factors which have nothing to do with the arrangement and magnitude of the electrical

* The term " C_5 pattern" is used for convenience. We have pointed out that in certain cases some neighboring position on the precordium may be the area which gives a pattern corresponding more closely to that of the left arm.

disturbances in the heart itself, *i. e.*, such factors as the electrical properties of the pathways between certain parts of the heart and the arms.* Thus far, we have not found additional advantage to be gained from Lead 1, yet the question may deserve further study.

Differences of potential between electrodes one of which is placed on the lower part of the body seem even more difficult to analyze than those obtained from two electrodes placed on upper parts of the body. It will require many more observations than have as yet been made, before they are well understood. We have shown that the C_1 and C_5 patterns can be demonstrated on certain parts of the abdomen and it is therefore probable that these (and possibly other anterior chest patterns) have some influence upon the potential variations of the legs. However, in a variety of electrocardiographic abnormalities, but especially in so-called posterior infarction, the altered electrical phenomena due to cardiac damage often appear to have an important influence on the potential variations of the lower part of the body surface and little observable influence above the diaphragm. In patients with posterior infarction, leads made between various paired areas both of which are above the diaphragm (such as Lead 1 or even a lead between C_5 and C_1) are apt to show little or no change from the normal; whereas in anterior infarction, leads from paired areas above the diaphragm often show marked abnormalities. However, when one electrode is placed below the level of the diaphragm, in a patient with posterior infarction, a pathologic pattern may be obtained.

It is obvious that the pathologic pattern of potential in posterior infarction must be derived from the changes in electrical activity produced by the lesion. The nearest fixed point to such a lesion where an electrode can be placed in a patient is in the lower end of the esophagus. Various workers⁵ have observed that when one electrode is placed in the lower esophagus, tracings can be obtained in cases of posterior infarction which show a definitely pathologic pattern. We have confirmed this observation (unpublished studies) and have studied the esophageal pattern by the methods of Equations 6 and 7 in 2 cases of healed posterior infarction. As compared with normals, initial negativity of the electrode in the lower esophagus during the QRS complex is apt to be greatly increased, its duration lengthened and the succeeding wave of positivity does not rise nearly so far above the isoelectric line (Fig. 5, B_1). Likewise there is negativity of the esophageal electrode during the inscription of the T wave.† These pathologic potential variations are much greater than any which can be obtained from the body surface in such cases.

At the present time one can merely speculate as to the major

* The importance of pathways within the chest can be demonstrated in patients with temporary pneumothorax or hydrothorax.

† The position of the electrode must be determined under fluoroscopic control in order to be certain that it is low in the esophagus. As stated above, in positions only a few centimeters higher, normals may show a similar pattern (Fig. 5, A_2).

source of ventricular potential on the lower part of the body surface. With the limited data in our possession we are inclined to the view that the part of the heart responsible for potential variation in the lower end of the esophagus is likewise responsible for an important part of the potential variation of the lower part of the body. Certainly the changes in lower esophageal leads and in leads made to positions below the diaphragm when posterior infarction is present, would support such a view. However, there is as yet no method for separating the "esophageal" pattern from the other patterns such as the C_1 and C_5 types in the lower part of the body, since we are unable to quantitate the values of the anterior chest patterns in these regions.

At least two attempts to register the potential variations of a single area have been recorded in the literature. The method of Wilson,¹¹ as is stated by the author, requires an assumption of the validity of the equilateral triangle hypothesis which our work, as well as that of Eyster³ and Katz⁶ has shown to be untenable. The immersion method of Molz⁹ requires the untested assumption that the potential of a salt solution bath in contact with the external body surface remains constant throughout cardiac contraction. In view of, (1) the structure of the body with surfaces in the lungs and gastro-intestinal tract which cannot be brought into contact with the salt solution, and (2) the different electrical properties of the various tissues, it would be naive to adopt such an assumption merely because it might hold in case of a technically perfect experiment dealing with homogeneous material of such nature that differences of potential between points could develop only on the surface which is in contact with the salt solution.

We have pointed out above that, provided an assumption is made, Equations 6 and 7 may be used to record the potential variations of a single area with approximate accuracy. This assumption is that no hidden pattern of potential variation is present in the various areas which were used as electrode positions in Equation 4. We have shown that if such a hidden pattern is present, it must be practically identical not only at both the C_1 and C_5 positions but at all other positions along each of the lines extending from C_1 to the tip of the right shoulder, and from C_5 to the left shoulder. Its distribution would therefore have to be through excellent conductors and entirely different from that of the C_1 and C_5 types of potential. This would seem to us to mean that this hypothetical "X" potential would have to arise from other parts of the heart than those from which the C_1 and C_5 patterns are derived. We do not, however, make the assumption that "X" potential is negligible even though there is reason to believe that such is the case.

Finally, it might be worthwhile to try to evaluate the new methods described in this paper. If there is no "X" potential, and if, therefore, we are able to measure, by means of Equations 6 and 7, the

potential variations of any given area on the body surface, the clarification of electrocardiographic conceptions which would result is obvious. Any given lead could be broken down into its two major components, which heretofore have been fused together indistinguishably. However, even if there is an "X" potential, some simplification may be attained. The principle may be discussed by taking Lead 2 as an example. For our present purposes, this lead may be considered as made up of three groups of potentials: (a) the "X" potential; (b) the C_1 pattern which has undergone decrement at a position so far away from the heart electrically as the right arm; and, (c) the potential variations of the left leg. By means of Equations 6 and 7, one group of variables, b, can be eliminated, and the tracing obtained will consist of only two groups of variables instead of three. Thus, if one desires to study the potential variations of the left leg, he can do it more accurately by means of Equations 6 and 7, than by means of Lead 2. So far as we are aware, this represents the first attempt to eliminate variables from electrocardiographic tracings which has not depended upon assumptions of questionable validity.

Summary. 1. Electrocardiograms made between small areas situated along a line drawn from the C_1 position to the tip of the right acromion (the right arm being regarded as an electrically intermediate position between the tip of the acromion and the axilla) all show a ventricular contour similar to Lead CR_1 , provided the same polarity is used in all these leads as in CR_1 . This we have called the C_1 pattern of potential. The size of the deflections seems to be related to: (1) the potential variations at the C_1 position; (2) the distance of the paired areas from the heart; and, (3) their distance from each other.

2. Electrocardiograms made between small areas situated along a line drawn from a position slightly outside the cardiac apex to the tip of the left acromion (the left arm being regarded as an electrically intermediate position between the tip of the acromion and the axilla) all show a ventricular contour similar to that of the CL Lead made to the position just outside the cardiac apex, provided the same polarity is used in all these leads as in the CL Lead. This we have called the C_s pattern, although it may be derived from the C_4 or C_6 position, depending on the relation of the cardiac apex to the chest wall. The size of the deflections seems to be related to: (1) the potential variations at the C_s position; (2) the distance of the paired areas from the heart; and, (3) their distance from each other.

3. By pairing appropriate areas along each of these two lines and making electrocardiograms with the same polarity as in Lead 1, a series of tracings closely resembling Lead 1 can be obtained. The deflections become larger as the paired areas approach the C_1 and C_s positions.

4. Various combinations of three positions can be found along

each of these two lines whose relationships are such that the ventricular potential of the intermediate position is approximately equal at all instants to the *mean* of the ventricular potentials of the proximal and distal positions.

5. The above-mentioned findings suggest that there is marked decrement in the C_1 pattern between the C_1 position and the right shoulder and also marked decrement in the " C_5 pattern" between the position just outside the cardiac apex and the left shoulder. However, there appears to be very little alteration in contour of either pattern along these radial lines from the precordium to shoulder tip.

6. By methods described in the text, combinations of three positions can be found along each of the two lines, whose relationships are such that the *sum* of the ventricular potential of the area nearest to the heart along one line plus that of the two areas further from the heart on the other line is approximately equal at all instants to the *sum* of the potentials of the other three areas. Furthermore, when such positions have been found, the relationships of the three areas on each side are such that the potential of the proximal area minus the sum of the potentials of the two distal areas on one side is approximately equal at all instants to the potential of the proximal area minus the sum of the potentials of the two distal areas on the other side.

7. On the basis of the above-mentioned relationships, the following may be demonstrated:

A. Lead 1 can be reproduced by the application of electrodes to various combinations of four chest positions without electrodes on either arm.

B. Either the C_1 pattern of potential is almost completely responsible for the potential variations of the right arm and the " C_5 pattern" of potential is almost completely responsible for the potential variations of the left arm, or else there is an additional pattern of potential variation common to all these areas which is not reflected in the tracings because it is identical at areas so near the heart as the C_1 and C_5 positions, and so far away as the right arm or tip of the right shoulder and the left arm or the tip of the left shoulder.

C. No matter which of the above alternatives is correct, Lead 1 represents the subtraction of the C_1 pattern of potential variation after it has undergone decrement, from the " C_5 pattern" after it has also undergone decrement.

D. If the first alternative stated above in "B" is correct, a method can be devised for recording the potential variations of ventricular origin in a single area. If the second alternative is correct, the method as described records the potential variations of a single area minus the hypothetical concealed pattern of potential common to all the areas mentioned in "B". Thus, no matter

which alternative is correct, the study of potential patterns can be simplified by the elimination of the obscuring effects of the C_1 and " C_5 patterns" present in upper parts of the body.

8. The presence of the C_1 and " C_5 patterns" of potential can be demonstrated below the diaphragm by appropriate methods. No test was made for other anterior chest patterns. The rather scanty evidence now available, however, indicates that a pattern or patterns of potential which seem to exert comparatively feeble effects above the diaphragm (at least in the formation of the C_1 and C_5 patterns) influence greatly either the potential variation of the lower part of the body or the hypothetical concealed potential not subject to decrement in the upper part of the body. From the practical point of view it would appear to make little difference which of these alternatives is correct.

9. Limited studies of the lower esophageal pattern of potential (below the level at which the electrode is in close contact with auricular muscle) suggest that the part of the heart responsible for this pattern has a marked effect on the form of the ventricular electrocardiogram when an area above the diaphragm (at some distance from the precordium) is paired with an area below the diaphragm.

10. The pattern of esophageal potential, at and above the level where the electrode is in close proximity to auricular muscle, resembles that which has been described as the endocardial pattern of potential variation more closely than it resembles the epicardial pattern. The effects of this pattern are probably not entirely negligible on the body surface.

11. The relationships among potential differences on the body surface resulting from cardiac electrical activity appear to be different from what Einthoven conceived them to be when he formulated the equilateral triangle hypothesis. The demonstration that certain patterns of potential variation found to exist in positions near the heart remain intact in positions far from the heart, except for decrement, and the relationships discovered as a result of these phenomena indicate the necessity for reconstructing electrocardiographic theory. An attempt has been made to begin this reconstruction.

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A CLINICO-PATHOLOGIC CORRELATION BETWEEN HEPATIC DAMAGE AND THE PLASMA PROTHROMBIN CONCENTRATION

By N. J. SWEET, M.D.,

RESIDENT PHYSICIAN, SAN FRANCISCO HOSPITAL,

S. P. LUCIA, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE,

AND

P. M. AGGELER, M.D.,

INSTRUCTOR IN PREVENTIVE MEDICINE, UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL,
SAN FRANCISCO, CALIF.

(From the Department of Medicine, University of California Medical School.)

EXPERIMENTAL data^{3-5,8-11} indicate that the liver is concerned in the production of prothrombin, and it has been suggested that the concentration of prothrombin in the plasma might be used, under certain circumstances, as a test of hepatic function. In patients suffering from damage to the liver, it has been observed that the concentration of prothrombin is usually diminished, and that it cannot be elevated by the administration of vitamin K.^{2,6} In most of the instances reported, the estimation of hepatic damage has been based solely on clinical evidence. In the present investigation, the determination of damage to the liver was ascertained by histopathologic study of material obtained at operation or at autopsy.

The prothrombin concentration was determined by the method of Quick.⁷ A concentration of 70% or greater was considered normal, since that value occurred in 98 of 100 normal subjects tested in our laboratory. In all patients with extrahepatic biliary obstruction, the recorded value of the prothrombin concentration was that obtained after the administration of an adequate dose of vitamin K. Details regarding the clinical course and response to vitamin K in many of these patients are recorded in previous communications.^{1,2,6}

The material for this report was selected from patients in whom a clinical diagnosis of disease of the liver was made, and some in whom there was no clinical evidence of hepatic damage. Patients in whom

the prothrombin concentrations were obtained within 1 day of death were included in the study because the results of these tests were in all instances consistent with previous determinations made on these same patients. We have not observed in any patient evidences of any specific agonal physiologic alterations in the prothrombin concentration. No case was included in this study where the last prothrombin concentration had been determined more than 30 days before death or operation. A further exclusion was made of all cases in which the clinical course or autopsy findings clearly indicated that the pathologic alterations observed in the liver were initiated or had progressed markedly subsequent to the last determination of the prothrombin concentration. An instance of this type of exclusion is that of the following case of a woman, aged 54, who developed a fulminating postoperative infection (*B. welchii*) of the liver and died within 24 hours; the infection had obviously occurred after the last determination of the prothrombin concentration which had been done on the day before operation.

In the 8 patients observed at the time of operation, a biopsy was taken and detailed notes were recorded of the gross appearance of the liver. In the 34 instances where autopsies were obtained, the gross appearance of the liver was recorded, and sections from many areas were obtained for histopathologic examination. An attempt was made to determine the relationship between the plasma prothrombin concentration and the type and extent of the pathologic processes observed. In each instance the pathologist designated the major histopathologic change, and estimated its severity without a knowledge of the prothrombin concentration.

Our results are given in Table 1. The prothrombin concentration was normal in 20 instances. Of these, 8 had no demonstrable damage to the liver, 3 had slight focal necrosis, 1 had slight passive congestion, 1 had marked fatty infiltration, 3 had cholangitis, 3 had slight portal cirrhosis, and 1 was diagnosed "hepatoma." In 22 instances the prothrombin concentration was diminished. Of these, 8 had various types of cirrhosis, 6 had primary or metastatic carcinomata, 4 had fatty infiltration, 2 had subacute yellow atrophy, 1 had miliary tuberculosis, and 1 was diagnosed as having "slight leukemic infiltration." In general, the prothrombin concentration was normal when there was little or no destruction of parenchymal tissue, and it was diminished when there was moderate or advanced destruction of parenchymal tissue. There were 2 subjects who deviated markedly from this rule. In 1 subject (Case 35) with extensive destruction of the liver by infiltrating hepatoma, the prothrombin concentration was 70%. In another subject (Case 42) with only slight leukemic infiltration, the prothrombin concentration 2 days before death was 40%. Subsequently a 50 mg. dose of phthiocol administered intravenously was without effect. Three hours before death the prothrombin concentration had dropped to 25%.

TABLE 1.—CORRELATION OF PROTHROMBIN CONCENTRATIONS AND HISTOLOGIC CHANGES.

Case No.	Age.	Sex.	Prothrombin concentration.		Time before autopsy or biopsy (days).	Autopsy, hrs. post-mortem.	Size of liver (gm.).	Histopathologic examination.	
			%.					Diagnosis.	Degree.*
1	67	F	70		4	$\frac{1}{2}$	1080	Normal	0
2	65	F	100		1	Biopsy	Normal	Normal	0
3	30	M	100		6	1	1780	Normal	0
4	31	M	90		1	Biopsy	Normal	Normal	0
5	38	F	100		1	Biopsy	Normal	Normal	0
6	58	M	80		4	2	1700	Normal	0
7	30	M	100		6	9	1880	Normal	0
8	69	M	85		4	$3\frac{1}{2}$	1460	Normal	0
9	38	F	70		13	$2\frac{1}{2}$	1570	Focal necrosis	+
10	63	F	90		1	1	1700	Focal necrosis	+
11	21	F	70		8	10	1170	Focal necrosis	+
12	53	M	70		20	10	1900	Passive cong.	++
13	61	M	65		5	14	1520	Fatty infiltr.	+
14	51	F	55		$\frac{1}{2}$	9	2200	Fatty infiltr.	+++
15	28	M	65		6	4	1600	Fatty infiltr.	+
16	50	M	60		4	$14\frac{1}{2}$	1600	Fatty infiltr.	+
17	40	F	70		4	6	1240	Fatty infiltr.	+++
18	65	F	75		$\frac{1}{2}$	$4\frac{1}{2}$	Normal	Cholangitis (mult. abs.)	++
19	61	F	70		7	10	1400	Cholangitis (occ. abs.)	++
20	47	F	80		30	18	1800	Cholangitis	++
21	34	M	55		4	15	2160	Toxic cirrhosis	+++
22	13	F	35		9	Biopsy	Normal	Toxic cirrhosis	+++
23	20	F	40		8	Biopsy	Normal	Toxic cirrhosis	+++
24	49	M	60		27	$1\frac{1}{2}$	1775	Toxic cirrhosis	+++
25	29	F	70		1	16	1180	Portal cirrhosis	+
26	57	F	90		1	Biopsy	Enlarged	Portal cirrhosis	+
27	32	M	65		3	Biopsy	Small	Portal cirrhosis	++
28	56	M	40		2	1	1400	Portal cirrhosis	++
29	42	F	90		11	Biopsy	Enlarged	Portal cirrhosis	+
30	37	M	50		2	$2\frac{1}{2}$	1560	Bil. cirrhosis	++
31	18	M	65		$\frac{3}{4}$	9 $\frac{1}{2}$	3000	Pigm. cirrhosis	++
32	37	M	25		1	11	1300	Subac. yellow atrophy	+++
33	62	M	20		1	2	800	Subac. yellow atrophy	+++
34	59	M	50		1	8	2200	Hepatoma	+++
35	53	M	70		29	4	2390	Hepatoma	+++
36	40	M	45		$\frac{1}{2}$	1	1780	Bile duct care.	+++
37	50	M	60		$\frac{5}{8}$	7	2700	Bile duct care.	+++
38	52	F	25		1	19	Markedly enlarged	Metast. carc.	+++
39	66	M	65		26	$11\frac{1}{2}$	2370	Metast. carc.	++
40	57	F	60		14	$8\frac{1}{2}$	2910	Metast. carc.	+++
41	44	F	50		15	$2\frac{1}{2}$	1750	Miliary tbc.	++
42	28	F	25		$\frac{1}{2}$	$\frac{1}{2}$	2230	Leuk. infiltr.	+

* 0 = none. + = slight. ++ = moderate. +++ = marked.

It is of interest that the prothrombin concentration was slightly diminished in 4 of 5 patients in whom fatty infiltration of the liver was the only abnormality noted. The prothrombin concentration was within normal limits in 3 patients with cholangitis, despite the fact that the inflammatory processes in the bile ducts were severe and had progressed in 1 instance to multiple abscess formation. However, in these latter cases the bulk of the parenchymal tissue appeared to be normal.

From these data there seems to be a better correlation between the prothrombin concentration and the histologic appearance of the liver than there is between the prothrombin concentration and the results of the hippuric acid liver function test.⁶ The obvious deduction from these observations would appear to be that of these two

tests the prothrombin concentration is the less sensitive indicator of liver function, but the more accurate detector of actual parenchymal hepatic tissue destruction.

Summary. The prothrombin concentration was determined in 42 patients in whom the liver was examined at operation or at autopsy. Vitamin K was administered in adequate dosage to all those patients who had suffered from extrahepatic biliary obstruction. In general, the prothrombin concentration was normal when there was little or no destruction of the parenchymal tissue, and it was diminished when there was moderate or marked destruction of tissue. Exceptions to this rule are noted.

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PLASMA AMINO-ACID LEVELS IN HEALTH AND IN MEASLES, SCARLET FEVER AND PNEUMONIA.

BY LEE E. FARR, M.D.,*

ASSOCIATE IN MEDICINE, THE HOSPITAL OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH,

WILLIAM C. MCCARTHY, M.D.,

RESIDENT, WILLARD PARKER HOSPITAL FOR CONTAGIOUS DISEASES,
AND

THOMAS FRANCIS, JR., M.D.,

PROFESSOR OF BACTERIOLOGY, NEW YORK UNIVERSITY MEDICAL SCHOOL,
NEW YORK, N. Y.

(From the Hospital of the Rockefeller Institute, Willard Parker Hospital for Contagious Diseases, Department of Hospitals, New York City, and the Department of Bacteriology, New York University Medical School.)

THE question of the constancy of blood amino-acid concentration in diseases other than those of the liver has been reopened with the finding of plasma hypoamino-acidemia in young children with the

* Present address: Alfred I. duPont Institute of The Nemours Foundation, Wilmington, Delaware.

nephrotic syndrome by Farr and MacFadyen² and in adults with pneumococcus pneumonia.⁴ This has been due in part to the development of a highly specific and accurate method for the estimation of amino-acids by Van Slyke, Dillon, MacFadyen and Hamilton⁵ and applied to blood and urine by MacFadyen, Van Slyke and Hamilton.⁶ By this method the plasma amino-acid concentrations of patients with scarlet fever, measles and pneumococcus pneumonia have been compared with those from a group of apparently healthy individuals.

Materials and Methods. Nine patients with scarlet fever and 12 with measles were observed in the Willard Parker Hospital for contagious diseases. Eighteen patients with pneumococcus pneumonia were admitted to the pneumonia service of the Rockefeller Institute Hospital under the care of Drs. C. M. MacLeod, G. S. Mirick, and E. C. Curnen. No attempt was made to select these patients for study and in each instance the series represents consecutive admissions. Thirty apparently healthy individuals were observed at the Rockefeller Institute Hospital. This group was highly selected and carefully examined by physical examination and laboratory studies to exclude insofar as possible any disease. Both adults and children were included in the normal group, the ages ranging from $\frac{1}{2}$ to 45 years. The patients with scarlet fever or measles were predominantly children, while those with pneumonia were all adults from 25 to 62 years with the exception of an 11-year-old boy.

Blood was obtained from all patients at the time of admission. Blood was withdrawn from the scarlet fever patients following an overnight fast thrice during the first week and subsequently at weekly intervals. A second blood specimen was obtained from patients with measles after 1 week. The patients with pneumonia were bled on admission, the day following, and at selected intervals thereafter. The procedures followed in taking the blood were as previously reported.⁴ On the 30 apparently healthy persons the blood was withdrawn after an overnight fast.

Plasma amino-acid nitrogen was determined by the ninhydrin CO₂ method of MacFadyen, Van Slyke and Hamilton.⁶

Results. The results are summarized graphically in Figure 1 and averages by each group with observed range and standard deviation are shown in Table 1.

TABLE 1.—AVERAGE PLASMA AMINO-ACID NITROGEN CONCENTRATIONS IN INDIVIDUALS WITHOUT APPARENT DISEASE, PATIENTS WITH PNEUMOCOCCUS PNEUMONIA, SCARLET FEVER, AND MEASLES.

	No. patients.	No. observations of plasma amino-acid nitrogen.	Average value plasma amino-acid nitrogen, mg./100 cc.	Standard deviation.	Observed range of plasma amino-acid nitrogen, mg./100 cc.
Normal persons	30	31	4.47	$\pm .46$	3.75–5.56
Pneumonia (at time of discharge)	18	18	4.11	$\pm .41$	3.29–5.16
Pneumonia (at time of admission)	18	36	3.10	$\pm .55$	2.25–4.49
Scarlet fever	9	29	4.25	$\pm .66$	2.97–5.59
Measles	12	18	4.05	$\pm .60$	3.19–5.27

In none of the 30 apparently healthy individuals was the plasma amino-acid nitrogen concentration below 3.75 mg. per 100 cc., and

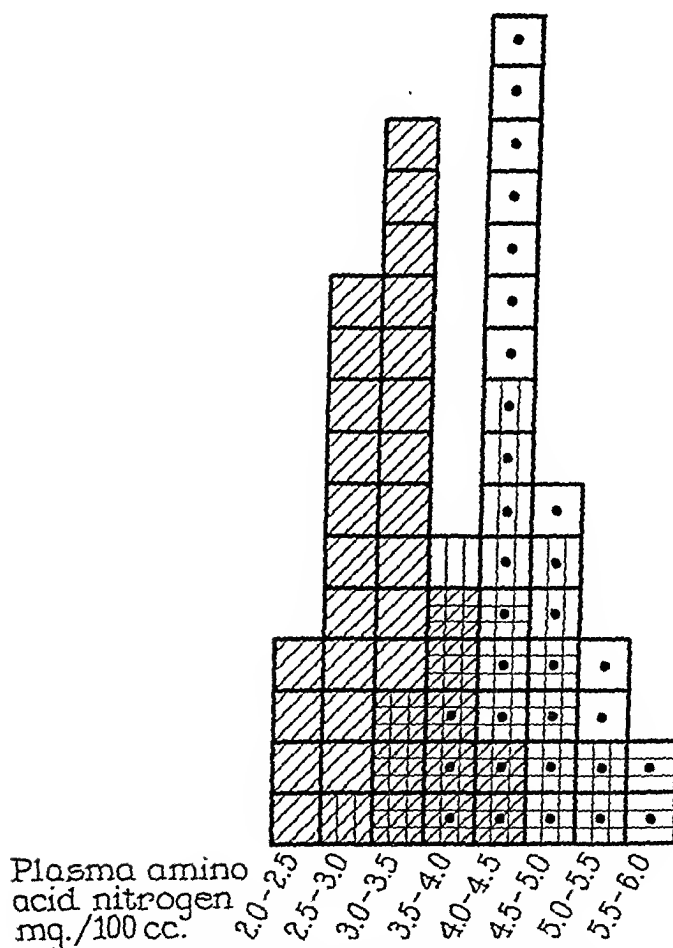
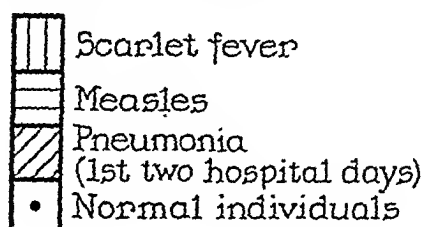


FIG. 1.—Distribution of fasting plasma amino-acid nitrogen values. Each square represents 1 patient, the varying markings indicating the type of patient.

in only 3 was the concentration below 4 mg. per 100 cc. The average plasma amino-acid nitrogen concentration in this group was 4.47 mg. per 100 cc.; the standard deviation was $\pm .46$, and

the observed range 3.75 to 5.56 mg. plasma amino-acid nitrogen per 100 cc. There was no apparent change in the plasma amino-acid nitrogen concentration with increasing age. Until further data are obtained we have taken 4.50 mg. per 100 cc. as the average plasma amino-acid nitrogen concentration of normal healthy persons and have assumed concentrations to be within normal limits when differing from the normal average by an amount less than, or equal to, twice the standard deviation.

With but 4 exceptions, the 29 determinations made on the 9 patients with scarlet fever fell within the range of concentration of the healthy individuals. Each of the 4 exceptions occurred in a different patient. In 1 patient a concentration of 3.37 mg. per 100 cc. was found on admission. Subsequent determinations made on plasma from this patient over a 2-week interval were 4.35 mg., 3.58 mg. and 3.66 mg. per 100 cc. The latter two values fall just within the range defined as normal. In addition to scarlet fever, this patient had pseudohypertrophic muscular dystrophy. Another patient in the scarlet fever group had a low plasma amino-acid nitrogen concentration of 3.31 mg. per 100 cc. which occurred at the time he developed serum disease. Determinations of plasma amino-acid nitrogen in this patient made during the week prior to development of serum disease were 4.70 mg. and 4.35 mg. per 100 cc. Seven days subsequent to the serum sickness the plasma amino-acid nitrogen concentration was 4 mg. per 100 cc. In 2 other patients single determinations, both made on admission, were 3.39 mg. and 2.97 mg. per 100 cc. In the first patient the plasma amino-acid nitrogen concentration rose during the following week to 4.61 mg. per 100 cc. and 1 week later was 5.59 mg. per 100 cc. No further estimations were made on the second patient.

In the 12 patients with measles, all but 1 of the 18 determinations of plasma amino-acid nitrogen concentration fell within the normal range. In this instance, the low concentration of 3.19 mg. per 100 cc. occurred at a time when the patient developed a rise in temperature with coarse rhonchi and râles over both lung fields but with no roentgenologic evidence of pneumonia. A previous determination on this patient was 3.86 mg. per 100 cc.

Of the 36 determinations of plasma amino-acid nitrogen made on 18 patients with pneumococcus pneumonia on the first and second day in the hospital, all but 7 were below the normal range. Of these 7, 2 were from a patient with a very mild illness. Of the remainder, the first blood sample was obtained from 5 different patients admitted on the fourth, sixth, seventh, eighth and ninth day of disease, respectively. As previously pointed out, a near normal value would be expected in such patients at this time. When discharged only 1 of the 18 patients with pneumonia had a plasma amino-acid nitrogen concentration below 3.5 mg. per 100 cc. She

had pulmonary tuberculosis and over a 2-month period of observation, her plasma amino-acid nitrogen concentration remained quite constant at about 3.30 mg. per 100 cc.

Comment. Although the values of plasma amino-acid nitrogen in patients with measles and scarlet fever were occasionally below the levels usually found thus far in normal individuals, it is evident from a study of the data presented that no significant plasma hypoamino-acidemia is usually associated with either scarlet fever or measles. This is in sharp distinction to our observations on patients with pneumococcus pneumonia and patients with the nephrotic syndrome.¹⁻³

The possibility exists that plasma hypoamino-acidemia was not observed in patients with scarlet fever or measles because the observations were not made sufficiently early in the disease course. The time of onset of pneumonia can be determined fairly accurately by the chill that occurs in most patients, whereas the diagnosis of scarlet fever or measles cannot be made with certainty during the preëruptive phase. An additional 24 hours usually elapses after the characteristic rash appears before the patient is brought to a hospital. Since in patients with pneumonia, the plasma amino-acids may return to near normal levels by the fifth day of disease, in this study we have not been able to exclude the possibility of a hypoamino-acidemia in scarlet fever and measles during the preëruptive phase.

The data in the present study cannot readily be compared to that of previous workers⁵ because of differences in the analytical methods used. In a majority of published studies, colorimetric procedures have been used which Van Slyke and Kirk⁸ have shown to be unreliable. The experiences of Farr and MacFadyen² with the Van Slyke nitrous acid method⁷ have shown that its lack of specificity in comparison with the ninhydrin CO₂ method may, under certain circumstances, give misleading results. A rational explanation for plasma hypoamino-acidemia in some diseases cannot be formulated until more is known of the mechanism controlling amino-acid metabolism and concentration.

Summary. Thirty-one determinations of the plasma amino-acid concentration of 30 normal, apparently healthy individuals averaged 4.50 mg. per 100 cc. by the ninhydrin-CO₂ method. The standard deviation was $\pm .46$, and the observed range 3.75 to 5.56 mg. per 100 cc.

In patients with pneumococcus pneumonia, the plasma amino-acid nitrogen concentration was found to be low at the time of onset. With recovery from pneumonia the plasma amino-acid concentration returned to the normal range. Patients admitted to the hospital after the fourth day of disease failed to show significant plasma hypoamino-acidemia.

In patients with scarlet fever and measles, the plasma amino-acid nitrogen concentration was usually within the normal range. How-

ever, because of the difficulty of ascertaining the time of onset of these diseases, the data do not exclude the possibility of a plasma hypoamino-acidemia during the preëruptive phase of these diseases.

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EOSINOPHILIC GRANULOMA AND CERTAIN OTHER RETICULO-ENDOTHELIAL HYPERPLASIAS OF BONE.

A COMPARISON OF CLINICAL, RADIOLOGIC, AND PATHOLOGIC FEATURES.

BY PAUL GROSS, M.D.,
PATHOLOGIST,

AND

HAROLD W. JACOX, M.D.,
RADIOLOGIST,
PITTSBURGH, PA.

(From the Institute of Pathology and Department of Radiation and Physical Therapy
of The Western Pennsylvania Hospital.)

FOLLOWING the first reference in 1929, additional cases of a certain peculiar, solitary, destructive lesion isolated in the skull and other bones of children and young adults have been described as a supposedly new disease under the names of eosinophilic granuloma or solitary granuloma of bone. In 1930, Mignon²⁸ described a "granulations tumor" in the forehead of a 12-year-old boy, and in 1938, Schairer³² reported 2 cases of "osteomyelitis with eosinophilic reaction." A publication by Otani and Ehrlich,²⁹ describing 7 cases, was quickly followed by Lichtenstein and Jaffe's²⁷ account of 4 cases. Hatcher¹⁷ observed 3 cases, Kernwein²¹ 1, and the Case Records of the Massachusetts General Hospital⁴ contained 1. Very recently Farber^{3a-c} listed 5 cases of solitary destructive lesions of granulomatous character in bone, and Bass,^{1b} in the latest publication on this subject, reported 2 cases and quoted Dr. R. H. Jaffe as having observed 1 case. Altogether 22 cases have been recorded in the literature. Of these, 12 have been described in more or less detail, the other 10 cases were merely mentioned as having been observed.

Unnecessary alarm may result and needless extensive surgery may be done unless the possibility of so-called eosinophilic granuloma of bone is kept in mind when sharply delimited, destructive, solitary bone lesions are encountered in children or young adults. Although a malignant process is frequently suggested roentgenographically, all reported cases have terminated by complete healing and cure.

Case Report with Solitary Lesion.* CASE 1.—A white schoolboy of 15 had noted a soft lump on the right forehead for 2 months. It had grown slowly to the size of a walnut and was accompanied by local pain and tenderness. There was no history of trauma and he was in excellent health otherwise.

The patient was a normal, asthenic type of youth with a movable, soft, tender swelling about 4 by 4 by 1 cm. in size situated 5 cm. above the right orbit in the frontoparietal region. The skin was not attached to it.

Roentgenograms of the skull (Fig. 1) showed a solitary, sharply-outlined, irregular, rounded area of bone destruction in the right frontoparietal region of 2.5 cm. in diameter. The inner table showed greater involvement than the outer, suggesting pressure from inside the cranium. The adjacent bone and the rest of the skull appeared normal. Although a definite diagnosis was not made, secondary neoplasm was considered. Careful search revealed no evidence of a primary tumor. Blood count, urinalysis and blood chemical examinations, including cholesterol, were not abnormal.

Exploration revealed friable, yellow, soft tissue, forming a mass about 4 cm. in diameter underneath the periosteum. Following removal of part of this tissue, a hole 1.5 cm. in diameter was seen in the skull through which the underlying dura and brain appeared normal.

As received in the laboratory the material consisted of several pieces of soft, pinkish-gray tissue which formed a mass 1 cm. in diameter.

Histologically, the tissue was composed of heavily vascularized reticulo-endothelial tissue profusely infiltrated by leukocytes and large mononucleated phagocytes. A large majority of the leukocytes were eosinophils, which, although diffusely distributed, were more densely congregated about vessels (Fig. 2). The nuclei of the stromal cells were large, somewhat variable in outline, with delicate nuclear membranes and finely divided chromatin material. Mitotic figures are absent. The cytoplasm of the stromal cells, while abundant, stained light pink and was, in many instances, foamy in character.

The large mononucleated phagocytes possessed rounded and well-defined cell walls while the nuclei resembled those of the stromal cells. The cytoplasm contained vacuoles, large, irregular granules, erythrocytes or eosino-

* We are enabled to report this clinical case through the courtesy of Dr. J. R. Johnston.

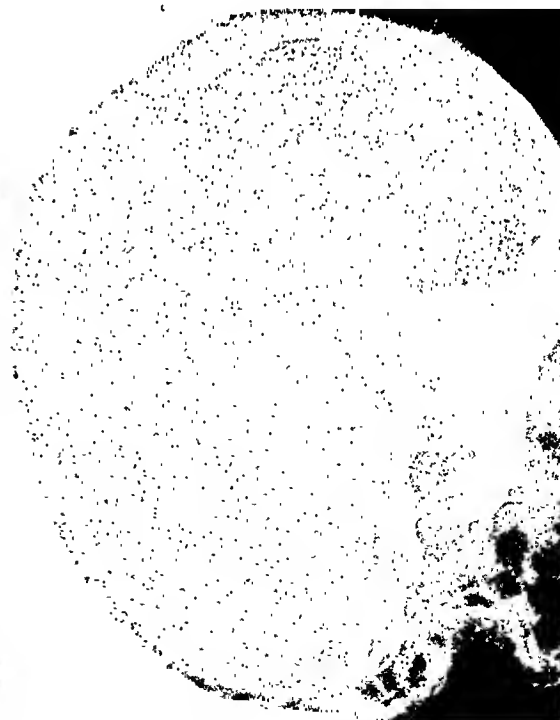
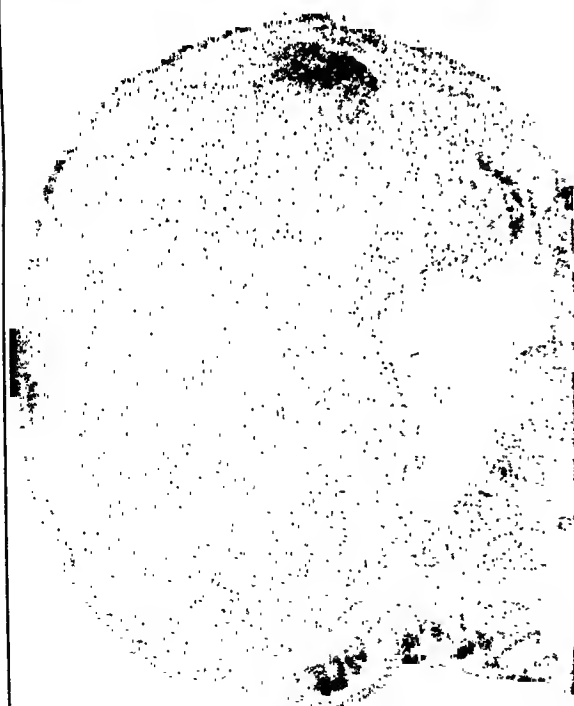
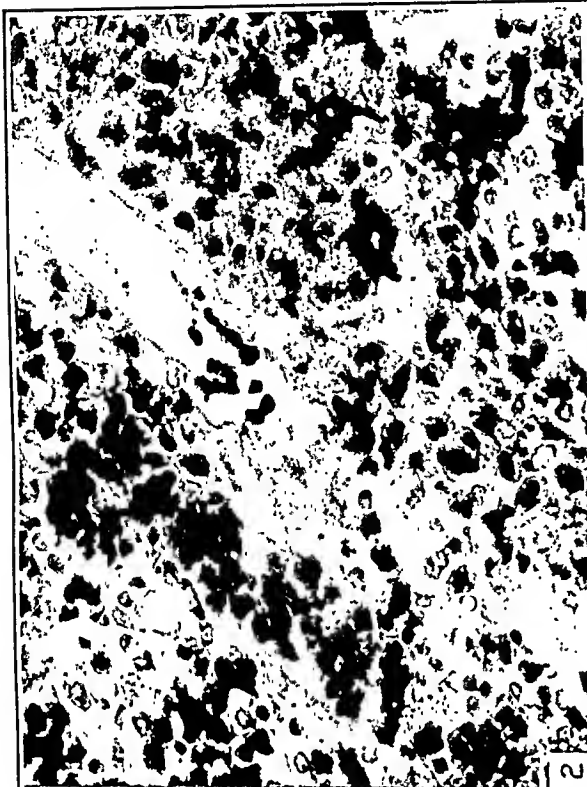
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FIG. 1.—Case 1. Lateral projection of skull showing a solitary, sharply-outlined, irregular, rounded area of bone destruction in the right fronto-parietal region.

FIG. 2.—Tissue from skull defect of Case 1, showing reticulo-endothelial tissue heavily infiltrated by eosinophilic polymorphonuclears (darkly staining cells). The infiltration is most pronounced about vessels. (Methylene blue-fuchsin stain.)

FIG. 3.—Case 1. Skull examination 16 months later, demonstrating complete healing and no new areas of involvement.

FIG. 4.—Case 2. Typical "geographic" skull as seen in Hand-Christian's disease.



philic granules. Occasional giant cells with peripherally arranged nuclei were found.

The vessels were thin-walled, frequently sinusoidal in type with large lumens. The endothelial cells lining the lumens were considerably swollen. Small hemorrhages were numerous.

Lymphocytes were infrequently seen. There were no areas of necrosis or fibrosis. No evidence of new bone formation was observed.

No bacteria could be demonstrated in the sections. Because the entire biopsy material was used for paraffin impregnation no fat stains were made.

Hand-Schüller-Christian's* disease and monocytic myeloma were considered as diagnostic probabilities and a number of prominent pathologists to whom the sections were submitted agreed with one or the other of these diagnoses.

About 2 weeks after operation a short course of high voltage Roentgen therapy was given. This consisted of a total of 1000 Roentgens (measured in air) applied in 5 daily exposures of 200 r each within a week to a field 6 by 8 cm. in size over the right frontal region.

Check-up examination 2 months after treatment showed alopecia over part of the treated area and a well-healed, depressed scar about 4 cm. in length. There were no other abnormalities.

At the last examination 16 months later, there was complete return to normal, both clinically and radiographically (Fig. 3).

Comment. Of the 16 recorded cases of so-called eosinophilic granuloma, in which the age was indicated, all but 3 were younger than 21 years. Of the latter, 1 was 21; 1, 24; and 1, 35 years old. Ten cases were male and 3 female. The sex of the other cases was not given. In 11 instances the lesion involved the skull; 5 of these, the frontal bone. The long bones were affected 5 times; ribs, 5 times; and the scapula, once. The bone lesions were commonly the only abnormality found and laboratory tests, with the exception of differential white blood cell counts, were normal.

Pain was mentioned as a prominent symptom in 7 cases. In 4 instances trauma to the site of the lesion was said to have antedated the appearance of the lesion. However, in several cases no history of trauma could be elicited, and in other reports no mention was made of trauma. The duration of the lesions, as indicated in the histories, varied from 10 days to 2 months.

The roentgenograms were commonly interpreted as suggestive of either osteomyelitis or tumor. In 6 cases subperiosteal bone formation was noted, while in 5 other cases notations were made of the absence of bone reaction.

A differential white blood cell count revealed a 4% to 11% eosinophilia in 7 cases. In one report³² eosinophilic infiltration was found in a lymph node near the lesion; in another instance²⁷ the sternal bone marrow showed an increase in eosinophils. Examination of the feces of 1 case¹⁰ disclosed a helminthic infestation which was regarded as the cause of the eosinophilia. Four reports noted a normal percentage of eosinophils in the peripheral blood.

* Hereafter the condition will be referred to as "Hand-Christian's" disease in keeping with preferable American usage.—EDITOR.

Grossly, the biopsy material from these lesions has been described as soft, cellular tissue, yellow-brown, gray-white, or gray-pink in color. With the exception of relatively minor details the histologic description in the various reports has been remarkably uniform.

The degree of phagocytic activity exhibited by the stromal cells, the presence or absence of multinucleated giant cells, mitotic figures, areas of necrosis, of scarring or of newly formed bone are details which vary somewhat in different reports. Such variance, however, may be explained on the basis that the biopsies represent different stages of the granulomatous process.

Before a lesion is classified as a separate and distinct pathologic entity, its distinguishing characteristics should be compared with those of related diseases in order to determine whether or not such segregation is justified.

The present study considers certain generalized hyperplasias of the reticulo-endothelial system as well as of the solitary xanthoma of bone which may be considered as a focal hyperplasia of reticulo-endothelial cells. Of the former, both the lipoid and non-lipoid varieties come under discussion.

Hand-Christian's Disease. This is usually a more or less generalized hyperplasia of the reticulo-endothelial system, of the lipoid variety. However, it is common knowledge that in this condition the classical triad—defects in the bones of the skull, diabetes insipidus and exophthalmos—may be incomplete. Indeed, some of the reported cases have none of these.

Other reported cases of Hand-Christian's disease raise the question of whether or not the reticulo-endothelial hyperplasia need necessarily be generalized. It seems possible, for instance, that in an early stage the disease may be represented by a solitary lesion. Such cases have been reported.^{6,25,31,41} In 1 of these²⁵ Schüller himself agreed with the diagnosis. Furthermore, Farber^{9b} encountered 4 instances of solitary bone lesions in which the patients later developed multiple lesions. The difficulty of differentiating this type of Hand-Christian's disease from the so-called eosinophilic granuloma, or the solitary xanthoma of bone is apparent. This difficulty was appreciated by Farber^{9a-c} who, following critical study, was led to conclude that eosinophilic granuloma of bone and Hand-Christian's disease "represent variations in degree, stage of involvement and localization of the same basic disease process."

As relatively few cases of eosinophilic granuloma of bone have been studied it would appear premature to state definitely that this lesion will always be solitary. Likewise, it would seem unreasonable to classify the eosinophilic granuloma of bone as a new and distinct entity because the lesion is solitary, and at the same time ignore its similarities or even its identity in other respects to related conditions. Our view, which is in full agreement with that of Farber,^{9a-c} is that the so-called eosinophilic granuloma of bone is probably

identical with what has been recognized as instances of Hand-Christian's disease in which the bone lesions are solitary.^{6,9b,25,31,41}

Case Report with Multiple Lesions. CASE 2.—A 4-year-old white girl was admitted to The Western Pennsylvania Hospital on January 25, 1934, suffering from a discharging left ear, prominence of the left eye and a stiff neck. The drainage from the left ear began a year and a half before admission, continued for 2 months and was followed by stiffness of the neck which lasted for 3 months. In the meantime the child apparently was well. One month before admission there was recurrence of the stiff neck, and a gradually increasing prominence of the left eye. Also at this time a soft spot on the left side of the child's skull and two small yellow spots in the left upper eyelid, not found previously, were first noticed.

The past and family histories were irrelevant.

The physical examination was negative except for the head, ears, eyes and neck. Several soft areas of various size were palpable in the frontal, parietal and occipital regions, suggestive of craniotabes. Both ears were dry, the canals being filled with soft wax plugs, but no pus was found when these were removed. Two small yellow intrautaneous plaques were found in the left eyelid. An ophthalmologist noted the left eyeball was slightly proptosed and displaced downward. There was 3 mm. of exophthalmos of the left eye as measured with the exophthalmometer (Hertel). The pupils, pupillary reactions and extraocular movements were normal. No palpable orbital masses were found, the fundi were not abnormal, and the media were clear. The child held the neck flexed and supported its head with its hands, but an orthopedic surgeon found motion of the cervical vertebræ free and without pain. A neurologist could demonstrate no neurologic syndrome.

Repeated blood counts showed a slight persistent eosinophilia (4%) but no other abnormalities. The Kahn test on the blood and spinal fluid of the patient as well as serologic tests of the mother and father were negative. The blood chemical examinations, including calcium, phosphorus and cholesterol were normal. Stool examinations and numerous urinalyses showed nothing abnormal. The highest temperature at any time was 37.4° C., but was usually normal.

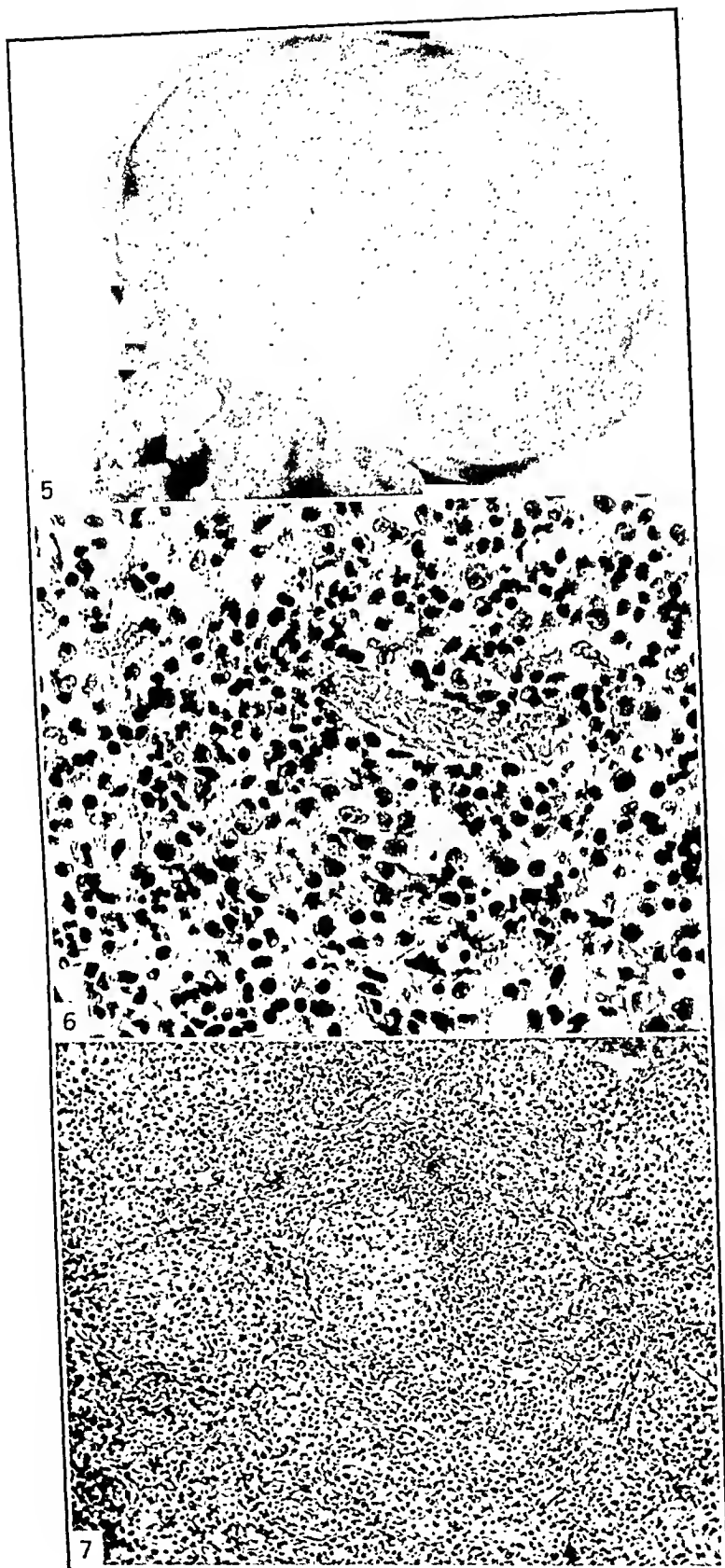
Skeletal roentgenograms revealed multiple destructive lesions of the skull and left femur. Numerous defects in these bones with smooth edges produced the typical "geographic" skull seen in Hand-Christian's disease (Fig. 4). There were extensive areas of decalcification in the frontal, parietal and basal regions, especially on the left side. One of the large destroyed areas extended into the left side of the foramen magnum and probably accounted for the discomfort and deformity in the cervical region. The normal bone architecture was gone in the area about the left mastoid

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FIG. 5.—Case 2. Skull 2½ years later with return to normal and no new areas. Condition remains the same after 7½ years. No direct irradiation was given over the frontal or parietal regions.

FIG. 6.—Tissue from skull defect of Case 2, showing reticulo-endothelial tissue profusely infiltrated by eosinophilic polymorphonuclears (darkly staining cells). The intercellular granular material is composed of eosinophilic granules from disintegrated leukocytes. No foam cells are present. (Hematoxylin and eosin stain.)

FIG. 7.—Lymph node from Case 3, showing replacement of most of the lymphoid tissue by proliferated reticulo-endothelial cells, diffusely and nodularly distributed. There is an associated increase in fibrous tissue. No foam cells are present. (Hematoxylin and eosin stain.)



process and no air-containing cells were found. In the lesser trochanter of the left femur were several irregular cystic areas of bone destruction. A Roentgen diagnosis of Hand-Christian's disease was made.

A biopsy specimen, about 2.5 cm. in diameter, and including the thickness of both tables, was obtained under ether anesthesia from one of the decalcified areas in the right parietal region of the skull.

A short course of high voltage Roentgen therapy was given 2 weeks later. This consisted of a total of 250 Roentgens to each of six long, narrow portals, cross-firing the neck and spine in 6 days. The lesions in the frontal, parietal and femoral regions received no direct irradiation.

The patient made a steady recovery, gained in weight and successive roentgenograms showed complete return to normal (Fig. 5). No new lesion ever appeared, and no further treatment was necessary. At the present time, $7\frac{1}{2}$ years later (July, 1941), the child is living and is normal except for diabetes insipidus, facial deformity and carious teeth. The diabetes insipidus has been present since an attack of whooping cough in 1936, but is now about half as bad as it was then. The urinary output varies from $3\frac{1}{2}$ to 7 liters per day at present.

The biopsy specimen consisted of soft, red tissue which measured 3 by 2 by 2 mm., and small fragments of bone.

Microscopically, the material was composed largely of dense collagenous tissue, the cellularity of which varied considerably in different fields. The greater portion of the collagenous connective tissue was poorly cellularized, relatively avascular and hyaline in character. There were, however, small, circumscribed areas, like little islands, which were composed of closely packed mononucleated phagocytes, polymorphonuclears and occasional lymphocytes. The majority of the leukocytes were eosinophilic (Fig. 6). Numerous eosinophilic granules, apparently derived from disintegrated leukocytes, were found between the cells and also within mononucleated phagocytes. The latter possessed abundant pale cytoplasm but without the slightest suggestion of foamy appearance. In contrast to the paucity of vessels in the adjoining tissue, these islands of inflammatory cells contained numerous congested capillaries.

Furthermore, portions of the dense connective tissue showed non-circumscribed infiltrations by a large number of lymphocytes and pyknotic, spindle-shaped cells. Adjacent to several of these infiltrations, trabeculae of bone were seen which showed loss of nuclei and pronounced decalcification. The edges of these trabeculae were marked by small, irregular defects which contained granular, acidophilic material. This gave the trabeculae a "moth-eaten" appearance.

In contrast to the above picture, a large trabecula of bone with a smooth and oval outline and otherwise normal appearance was seen only a few low-power diameters away from the regions of bone destruction. The periphery of this trabecula was delimited by a zone of closely applied, scattered osteoblasts and by dense periosteum-like tissue. The surrounding collagenous connective tissue was relatively acellular and avascular. In short, the picture in this region was that of quiescence and complete healing.

No evidence of new bone formation was seen. The destroyed bone was apparently replaced by dense collagenous tissue. No giant cells were found in the sections. No examination was made for the presence or absence of lipoids or fat.

Comment. The similarity microscopically between the lesion of the second case and that of the first is striking. Probably the greatest difference is in the presence of scar tissue in the second, and the absence of dense collagenous tissue in the first case. The difference

is readily explained by a difference in the stage of the disease process as indicated by Farber.^{9a-c} The small cellular islands found in the second case represent active foci of the disease and they are absolutely identical with the type of tissue found in the first case.

Our belief in the probable identity of the two diseases is based mainly upon the fact that the histologic features regarded as characteristic of eosinophilic granuloma of bone are also found in Hand-Christian's disease. Both conditions show destruction and replacement of normal tissues by granulomatous tissue in which endothelial cells predominate. The latter may contain lipid. In an analysis of 84 cases of Hand-Christian's disease reported in the literature, we have found 9 in which lipid-containing cells or "foam cells" were not found in the biopsy or autopsy material and in 26 cases neither the presence nor the absence of these cells was mentioned.

The participation of eosinophilic leukocytes is common to the lesions of both conditions. It was noted in 29 of the 84 cases of Hand-Christian's disease analyzed by us and in 5 of 7 such cases studied by Farber.^{9b} Not infrequently this eosinophilic infiltration was regarded as pronounced.

Eosinophilia of the peripheral blood has been noted with eosinophilic granuloma.^{4,10,27,28,32} In the 84 cases of Hand-Christian's disease analyzed by us eosinophilia was noted in 13 cases; 3% in 3,^{7,36,37} 4% in 5,^{2,20,24,30,40} 5% in 1,⁵ 6% in 3^{9b,19,25} and 7% in 1 case.¹⁴

Hand-Christian's disease is, at times, associated with a hypercholesteremia. Out of a total of 45 in which the blood cholesterol content was indicated, 23 cases had a level of over 200 mg. per 100 cc. Insufficient data are available regarding this point in eosinophilic granuloma of bone.

Visceral involvement in Hand-Christian's disease is common. It is interesting to note that we have found 2 cases^{23,30} in the literature in which there was soft tissue involvement but no radiologic evidence of bone lesions. Since no autopsies have been performed on cases of eosinophilic granuloma of bone, little can be said about visceral involvement in this condition. However, reports of eosinophilia in a draining lymph node,³² in sternal bone marrow,²⁷ as well as in the peripheral blood^{4,10,27,28,32} indicate that in addition to the solitary osseous lesion in eosinophilic granuloma of bone there may be more widespread and even systemic changes.

In both types of lesions various stages of healing with the production of osteoid tissue and bone may be encountered. There may be very little of pathognomonic significance and no essential difference in the histologic appearance of the lesion of either condition. As a matter of fact, some radiologists have discouraged biopsy in Hand-Christian's disease because the histologic picture of the lesion in this disease has been nondescript and inconclusive on occasions.

The radiologic appearance of the osseous defects in Hand-Christian's disease is very similar to that of eosinophilic granuloma. The

only difference appears to be that in the former the lesions are usually multiple and in the latter disease there is a solitary lesion.

As in Hand-Christian's disease the lesion of eosinophilic granuloma may progress spontaneously or with irradiation. Unlike the 30% case mortality of Hand-Christian's disease, all reported cases of eosinophilic granuloma have recovered.

Letterer-Siwe's Disease. This is a non-lipoid reticulo-endotheliosis considered by some writers identical with infectious reticulo-endotheliosis. It has certain similarities to Hand-Christian's disease and to eosinophilic granuloma. Letterer-Siwe's disease affects infants and children predominantly and is nearly always fatal. From a radiologic point of view the osseous lesions of this disease are identical with those of Hand-Christian's disease. Histologically, the lesions are usually devoid of lipoid, but cases^{8,39} have been reported where small amounts of lipoid were present within the reticulo-endothelial cells. On the other hand, biopsies from lesions of Hand-Christian's disease may also show little or no lipoid.

Case Report of Non-lipoid Reticulo-endotheliosis.* CASE 3.—A 13-month-old, white, female infant was admitted to the St. Vincent Charity Hospital of Cleveland because of splenic and generalized lymph node enlargement.

The past history was not significant except that for 6 months previously the infant had been eating poorly and for a number of days prior to admission there had been dyspnea at night.

The patient's weight on admission was 7550 gm. (16.6 pounds). There was a discharge of partially crusted material in both external auditory meati. The drums were hyperemic. Examination of the chest disclosed no abnormality. The spleen was enlarged and extended 4 cm. below the costal margin. The cervical, axillary and inguinal nodes were enlarged and discrete.

The red blood cell count varied from 4.2 to 2.5 million during hospitalization. The concomitant hemoglobin determinations varied from 72% to 34%, and the platelet counts from 270,000 to 366,000. There was no eosinophilia.

During hospitalization the infant had successive showers of cutaneous petechiæ. The spleen enlarged progressively and reached to the iliac crest shortly before death. The lymph nodes also became larger.

Roentgenologic examination of the chest disclosed enlargement of the thymus and a diffuse mottling in the lung fields, suggestive of miliary tuberculosis.

The temperature varied between 37.5 and 38.5° C. with occasional peaks of 39.5°, and a terminal rise to 41°. Death occurred 5 months after admission.

A biopsy of a cervical lymph node performed 3 months before death showed a remarkable degree of endothelial hyperplasia which was diffuse and nodular. Many giant cells were present. This appearance was mistakenly interpreted as that of hyperplastic tuberculosis.

The significant *autopsy* findings consisted of the following:

Innumerable cutaneous petechiæ were present.

The thymus was much enlarged and its normal, lobulated architecture

* Presented by one of us (P. G.) before the Clinical and Pathological Section of the Academy of Medicine of Cleveland, May 4, 1934.

replaced by trabeculated hemorrhagic tissue which contained irregular yellow foci.

The lungs were honeycombed by smooth-walled cysts 3 to 7 mm. in diameter and the lower lobes were consolidated.

The liver was enlarged and showed fatty change.

The spleen was greatly enlarged, rounded, blue-red in color, firm in consistency. The cut surface showed a variegated red and yellow, firm, somewhat trabeculated tissue which replaced the normal splenic architecture. The yellow areas were in the form of miliary and larger conglomerate nodules.

Lymph nodes, everywhere, were enlarged and on section showed small, opaque yellow foci.

The lymphoid apparatus throughout the intestinal tract was tremendously hypertrophied.

Postmortem roentgenograms of the skull showed defects in both parietal bones. The largest was about 2 cm. in diameter.

Microscopically, sections of spleen, liver, lymph nodes, thymus, lung and intestinal tract showed replacement, or infiltration, or both, by cells of the endothelial type. In addition to a diffuse type of infiltration, nodules resembling those seen in Boeck's sarcoid were present in lymph nodes, spleen and thymus (Fig. 7). In these organs the endothelial hyperplasia was also associated with a pronounced increase in fibrous tissue particularly in the capsule and pericapsular region. In the liver and lung the proliferation of endothelial cells was less striking, but, nevertheless, pronounced. There was associated, extensive fatty metamorphosis throughout the liver while the lung exhibited irregular thickening of alveolar walls and peribronchiolar tissue by proliferated endothelial cells which resulted in numerous large, cyst-like, emphysematous cavities. A considerable portion of both lungs, particularly throughout the lower lobes, showed more diffuse infiltration by endothelial cells, which filled the alveolar spaces and gave the tissue the appearance of pneumonic consolidation.

The proliferated endothelial cells were frequently large, oval, rounded, or polygonal, and possessed deeply acidophilic cytoplasm. Some cells contained hemosiderin. No foam cells were found. A pronounced tendency to form many multinucleated giant cells was present in the spleen and thymus. This was less marked in the lymph nodes and lung, and absent in the intestinal tract and liver. The spleen and thymus also exhibited many mitotic figures and considerable pleomorphism of the endothelial cells as well as many areas of necrosis and hemorrhage. These changes suggested a transcendancy of hyperplasia to neoplasia. However, the absence of such changes in the proliferated endothelial cells elsewhere and their relative uniformity in other organs gave the impression that the original and indeed, the picture as a whole was that of simple hyperplasia.

Silver impregnation stains showed a pronounced increase in the reticulum, the fibers of which frequently tended to surround the individual endothelial cells.

The Sudan IV stain revealed that occasional cells were filled with fine droplets of fat, some cells contained only a few droplets while the vast majority of the proliferated cells contained no stainable fat.

Comment. The clinical syndrome exhibited by Case 3 of lymph adenopathy, splenohepatomegaly, cutaneous petechiæ, bone defects, hypochromic anemia, fever and rapid down-hill course includes practically all the important features of Letterer-Siwe's disease (non-lipoid reticulo-endotheliosis).

The microscopic picture, with the exception of neoplastic changes

in the spleen and thymus, is clearly consistent with this concept. It is not unusual in this disease to find small amounts of fat in the proliferated endothelial cells. The pulmonary changes of Case 3 have been more commonly seen in Hand-Christian's disease. The sarcomatous changes in the thymus and spleen are considered incidental and terminal.

The difference between the lipid and the non-lipoid varieties of reticulo-endotheliosis may, on first impression, seem adequate. However, a study of the reported cases reveals, as Wallgren³⁹ has stated, that these differences are not greater than the variations in pathologic anatomy between different cases of the same disease. He further emphasized that neither of the two diseases has any characteristic feature that cannot occur in the other. What seems to us a logical view is expressed by both Wallgren³⁹ and Glanzmann,¹³ who look upon Hand-Christian's disease as the chronic form, and upon Letterer-Siwe's disease as the acute form of reticulo-endotheliosis. The paucity of lipid in Letterer-Siwe's disease is explained on the basis of its rapid course.

The connecting link between Letterer-Siwe's and Hand-Christian's disease is formed by those cases^{11,15,18,35} possessing features intermediate between the two diseases. Several of these^{15,35} exhibited eosinophilic infiltration as a component of the osseous lesions. The connecting link between Letterer-Siwe's disease and eosinophilic granuloma of bone is represented by the case reported by Guizetti.¹⁶ A 3-month-old infant had a solitary lesion of the humerus which showed the histologic picture of eosinophilic granuloma of bone. In addition, the body of this infant showed visceral lesions characteristic of infectious reticulo-endotheliosis.

Solitary Xanthoma of Bone. We have found in the literature 7 cases of solitary xanthomatous lesions of bone. In 5,^{3,22,33,34,38} the histologic diagnosis or description indicated the presence of lipid granulomatous tissue in the lesion. One¹² was said to be a pure xanthoma without admixture of granulomatous aspects and another²² was said to be a "typical xanthoma" which, in addition, contained an abundant amount of hemosiderin. In 3 cases^{3,22,142} the blood cholesterol was elevated: 224 mg., 274 mg., and 300 mg., per 100 cc., respectively.

The presence or absence of eosinophilic leukocytes in the lesion was not mentioned by any of the reporters. Inasmuch as the infiltration by eosinophilic leukocytes was either not mentioned or treated very casually in most of the reports dealing with Hand-Christian's disease, little significance can be attached to this omission in cases of solitary xanthoma of bone.

From a histopathologic point of view there may be nothing else to differentiate this type of lesion from that of eosinophilic granuloma or of Hand-Christian's disease. Roentgenologically, no significant difference may exist between the appearance produced by the lesions of

solitary xanthoma, eosinophilic granuloma and the individual lesions of Hand-Christian's disease and Letterer-Siwe's disease.

Prognosis. Given a patient with a solitary bone defect of the type seen in the reticulo-endothelioses a biopsy is necessary to establish the probability as a fact. If the microscopic picture is that of lipid reticulo-endotheliosis, the lesion heals, and if no subsequent ones appear within a year the chances that the patient is cured are good. If, however, other lesions develop there is approximately a 30% probability of a fatal outcome.

If the microscopic picture is that of non-lipoid reticulo-endotheliosis, Hand-Christian's disease cannot be ruled out because lesions elsewhere in the body may be quite characteristic of the latter.^{12,15} However, if the osseous lesions are associated with an acute and rapidly progressive clinical course characteristic of so-called non-lipoid reticulo-endotheliosis the probability of a fatal issue is nearly 100%.

General Considerations. Of the various lesions under discussion those of Hand-Christian's disease are the most common. Nevertheless, even the latter is so infrequently encountered that the average pathologist has little familiarity with it. It is not surprising to find that this disease has been diagnosed tuberculosis, osteitis-fibrosa, luetic osteitis, carcinoma, sarcoma and multiple myeloma.

On the other hand, the literature also contains statements which imply considerable confidence in ability to arrive at the correct diagnosis. The statements "no other condition causing destructive lesions in the skull in children has simulated it" (Hand-Christian's disease), and "the diagnosis was uncertain until x-ray showed the presence of Hand-Christian's disease" indicate that either the writers were not familiar with other reticulo-endothelioses or they considered the latter identical with the former.

The presence of small amounts of lipid in the endothelial cells does not exclude non-lipoid reticulo-endotheliosis. How much lipid a lesion of this disease may contain and still deserve its classification has not been defined. It has been customary to classify the lesion as lipid reticulo-endotheliosis if "foam" cells or cholesterol-needle spaces are present.

It appears that our knowledge of the diseases involving reticulo-endothelial proliferations, whether focal as in eosinophilic granuloma or solitary xanthoma, or more generalized as in Hand-Christian's disease or Letterer-Siwe's disease, is far from complete. Biopsies should therefore be encouraged rather than discouraged.

The similarity in histopathologic features of eosinophilic granuloma on the one hand and solitary xanthoma as well as Hand-Christian's disease on the other, is quite close and warrants placing these conditions in the same general disease group.

There does not seem to be any observed distinctive roentgenographic or pathologic feature nor other decisive information at

present regarding any one of these lesions to justify their dogmatic segregation into separate disease entities.

Likewise, the existence of cases with features intermediate between Hand-Christian's disease and Letterer-Siwe's disease (or infectious reticulo-endotheliosis) raises the question of whether or not a sharp distinction between the lipoid and the non-lipoid reticulo-endothelioses is valid.

Conclusions. 1. Eosinophilic granuloma of bone is not a new nor distinct entity. It is a reticulo-endotheliosis and is probably identical with those cases of Hand-Christian's disease which have been reported to have had solitary lesions. It is also closely related to certain other reticulo-endothelial hyperplasias.

2. The interrelationship demonstrated between eosinophilic granuloma and solitary xanthoma of bone, Hand-Christian's and Letterer-Siwe's disease and the existence of cases with features intermediate between these so-called entities make sharp distinctions between them of doubtful validity.

3. Since there are no pathologic, roentgenographic or other decisive features known at present which are distinctive for any one of these reticulo-endothelioses, the need for further study, including routine biopsy, in this type of case is apparent.

4. Three case reports are presented which illustrate the variations in degree, stage of involvement and localization of reticulo-endotheliosis.

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THE TOXICITY OF FLUORINE IN DICALCIUM PHOSPHATE.*

By FLOYD DEEDS, PH.D.,

PRINCIPAL PHARMACOLOGIST,
SAN FRANCISCO, CALIF.

(From the Agricultural Chemical Research Division, Bureau of Agricultural Chemistry and Engineering, United States Department of Agriculture, at the Department of Pharmacology, Stanford University School of Medicine.)

DICALCIUM phosphate is used as a dietary supplement during pregnancy, and for infants and children. Since fluorine is present in dicalcium phosphate as an impurity due to the sources of raw material or methods of manufacture, obstetricians and pediatricians should give consideration to the possibility of chronic fluorine poisoning.

It appears unlikely that a contamination as great as 0.5% or 5000 parts per million, would be encountered in dicalcium phosphate prepared by a responsible manufacturer. However, even such a high degree of contamination would not be likely to cause acute fluorine poisoning, since a dose of 2 to 4 gm. of dicalcium phosphate would represent an intake of only 10 to 20 mg. of fluorine. An acute reaction would be all the more improbable because of the large excess of calcium. Therefore, the problem requiring attention is one of chronic poisoning which differs from acute fluorine poisoning both as to symptoms and mechanism of action.

An interesting feature of fluorine toxicosis is the difference in symptomatology and mechanism of action between acute poisoning and chronic poisoning produced by continued ingestion of fluorides over a period of time. For the purpose of this report interest in acute fluorine poisoning centers in the fact that an acutely toxic dose of fluoride lowers the level of blood calcium and produces the symptoms characteristic of a decrease in blood calcium. The administration of calcium chloride or lactate is a satisfactory anti-

* Agricultural Chemical Research Division Contribution No. 32.

dotal measure. In sharp contrast is the fact that chronic fluorine poisoning resulting from continued ingestion of fluorides is not characterized by a drop in the blood calcium level. Moreover, there is no conclusive evidence that calcium administration alleviates the symptoms of chronic fluorine poisoning.

The most striking and most easily observed symptom of chronic fluorine poisoning is bleaching of tooth enamel, known as enamel dystrophy or mottled enamel. This dental defect has been repeatedly demonstrated in rats and dogs, and occurs in man under conditions where fluorine has been ingested more or less continuously in the drinking water during the time that the permanent teeth were being laid down. While this dental defect is the most readily observed injurious effect produced by the continued ingestion of fluorine, it is by no means the only undesirable effect. The review by Kaj Roholm⁹ presents adequate evidence of the deleterious effect of fluorine on the bony structures in general.

Evidence obtained both *in vivo* and *in vitro*¹ in this laboratory strongly suggests that the fundamental mechanism involved in chronic fluorine poisoning is an inhibitory action on bone phosphatase activity. The recent report by Wilson, DeEds and Cox¹⁵ on cadmium toxicity lends support to the idea that an inhibition of phosphatase activity is intimately associated with the impairment of calcification. It was shown by Wilson and DeEds that the continued ingestion of cadmium by albino rats produced a bleaching of the incisors indistinguishable from that caused by fluorine. The possibility that the bleaching of rat incisors might be caused by a sensitization of the rats to the action of small amounts of fluorine normally present in the diet, rather than to the cadmium *per se*, was not conclusively ruled out. However, the demonstration *in vitro* that cadmium in a concentration of 10^{-3} N equivalent to 112 parts per million, reduced the activity of a bone phosphatase preparation to 8% of the activity in the absence of cadmium, strongly suggests that cadmium *per se* can produce the same lesions in bony structures as does fluorine.

If the cation cadmium *per se* can produce the same defect in tooth enamel that is produced by the anion fluorine, it seems unlikely that the defect is due to a deficiency of calcium. A more fundamental mechanism must be postulated to account for an abnormal calcification produced by either a cation or an anion. The important deduction to be made is that an abundant or excessive intake of calcium might not be expected to counteract the toxic action of continuously ingested fluorine.

Present Studies. An excellent test of the effect of an increased calcium intake on the chronic toxicity of fluorine is the determination of the toxicity of fluorine as found in dicalcium phosphate.

A patent has been granted to M. H. Merchant⁴ for the removal of fluorine compounds from bone liquors. It is pointed out in this

patent that the fluorine content of dicalcium phosphate as ordinarily prepared from bone liquors may run as high as 1000 parts per million, or even more, and that good dicalcium phosphate of commercial grade preferably contains not more than 0.03%, or 300 parts per million. Merchant states that, since fluorine is considered objectionable in foods, or in chemicals to be used for human consumption, it is desirable to reduce the fluorine content of dicalcium phosphate to as low a value as possible, such as 20 to 40 parts per million.

The sample of dicalcium phosphate used in this study was supplied by the Food and Drug Administration. Their analyses showed a fluorine content of 0.27%, or 2700 parts per million. The possibility of a toxic action traceable to the fluorine in the dicalcium phosphate was tested by incorporating the material in various concentrations in a well balanced diet¹⁶ and feeding it to groups of albino rats.

Twenty albino rats (12 females and 8 males) were divided into four groups containing 3 females and 2 males each. All the rats were of approximately the same age, being born within a period of 5 days. The rats were quite uniform in weight (average, 41.7 gm.). Each group of rats was placed in a cage permitting free access to water and food at all times. Four diets were prepared containing 3, 6, 12, and 24 gm. of dicalcium phosphate per kilo of diet, corresponding to 8.1, 16.2, 32.4, and 64.8 parts of fluorine per million parts of diet respectively. One group of rats was placed on each of these diets, and observations were made on an average of once a week for changes in the coloration of the incisor teeth.

When the incisor teeth of the young albino rat first erupt they are completely white. Even at the age of 30 days, when the rats weigh 40 to 50 gm., the incisor teeth have little of the color characteristic of the adult rat. During the next 20 to 30 days the anterior enamel surface of the incisors darkens rapidly until it reaches the depth of color seen in the normal adult rat. The final increase in coloration is a slow process.

The fluorine present in all dosage levels of dicalcium phosphate used adversely affected the normal rate of coloration of the rat incisors. A concentration of 0.3% dicalcium phosphate, corresponding to 8.1 parts of fluorine per million parts of diet, slightly retarded the rate of tooth coloration for the first 30 days and subsequently actually produced a definite degree of bleaching as compared with the controls. Doubling the concentration of dicalcium phosphate gave a fluorine concentration of 16.2 parts per million and caused a bleaching of the rat incisors as early as the 15th day. The bleaching developed rapidly after the 30th day. Levels of dicalcium phosphate corresponding to 32.4 and 64.8 parts of fluorine per million parts of diet produced a final degree of bleaching only slightly more severe than that resulting from 16.2 parts of fluorine per million, but the bleaching action became evident much

earlier, especially on the highest fluorine intake where little coloration of the incisors appeared at any time.

The dosage levels of dicalcium phosphate used were determined by the known fluorine content, and the previously reported fact² that 14 parts of added fluorine, in the form of sodium fluoride, per million parts of diet produced unmistakable bleaching of rat incisors in all rats. The obvious conclusion from the results in this report is that the fluorine content in dicalcium phosphate is as readily available for production of chronic toxicity as is the fluorine in sodium fluoride. The calcium and phosphate had no demonstrable antidotal effect. The results support the claim that chronic fluorine poisoning is not associated with calcium depletion.

Possible Clinical Significance. For purposes of supplementing the diet with calcium and phosphorus, the recommended daily dose of dicalcium phosphate for a period of weeks or months is $\frac{1}{4}$ to 1 teaspoonful for infants, and $\frac{1}{2}$ to $1\frac{1}{2}$ teaspoonsful for children. Let us assume that the average daily dose of dicalcium phosphate is 1 teaspoonful, or approximately 60 grains, equivalent to 3.8 gm. The dicalcium phosphate sample used in this investigation had a fluorine content of 0.27%. This means that the average daily dose of approximately 4 gm. of dicalcium phosphate would represent a daily fluorine intake of 10 mg. Moreover, it must be borne in mind that this fluorine intake is superimposed upon that which is unavoidably ingested with food and water, and which represents a variable and unknown amount. It has been reported that drinking water containing 1 part of fluorine per million can produce mottled enamel in children. If the average daily consumption of such water is assumed to be 1 liter, approximately 1 quart, it is seen that a daily fluorine intake of 1 mg. produces mottled enamel in at least some children. Therefore, an average daily dose of 1 teaspoonful of dicalcium phosphate having a fluorine content of 0.27% represents a fluorine intake 10 times the amount known to be injurious to the teeth. This conclusion is supported by the results of this investigation which have shown that the fluorine in dicalcium phosphate is as physiologically active as is fluorine in sodium fluoride.

A brief review of the pertinent reports in the literature on fluorosis will supply the background of information which, from the viewpoint of the obstetrician and pediatrician, gives added significance to the results herein reported. These reports are concerned with the maternal transfer of fluorine, the effects in the newborn and on the deciduous teeth, evidence on the mechanism of fluorosis, and evidence for effects other than the production of mottled teeth.

In an earlier report from this laboratory¹ it was shown that the bones of young rats suckled by mothers receiving sodium fluoride in the diet exhibited a decrease in phosphatase activity as compared with controls. In harmony with this observation is the report by Robison and Rosenheim⁸ that a concentration of 0.00001 M

sodium fluoride in the perfusion liquid inhibits calcification *in vitro*. Murray⁵ has reported that the average fluorine content of the bodies of five litters of rats born of mothers receiving 0.05% sodium fluoride in their diet was significantly higher than the average fluorine content of five litters born of normal mothers. Murray concluded that the amount of fluorine transferred *in utero* was large enough to be harmful in the light of the calcification studies by Robison and Rosenheim.⁸ Murray⁵ has also demonstrated the transference of fluorine during lactation. The possibility of fluorine poisoning during uterine life has also been investigated by Velu¹³ who concluded that young animals born from mothers exposed to the influence of fluorine develop dental alterations which must have originated during the time before birth. Smith and Smith¹¹ have reported on the occurrence of mottled enamel on the temporary teeth of children living in a district where the water supply contained from 12 to 18 parts of fluorine per million. However, these authors state: "Severe mottling of the enamel of the temporary teeth has since been found in the breast-fed infants. This points to the passage of fluorine into the fetal system or into the milk supply of the nursing mother. Again, the fluorine concentration of the water supply was found to be excessively high."

It is outside the scope of this report to review all the evidence related to the changes in teeth and bone produced in chronic fluoride poisoning. For a more detailed account and references the reader is referred to the excellent review of Kaj Roholm.⁹ However, the conclusions of several investigators may be given. For instance, Sutro¹² studied the changes produced in rats and concluded that the changes produced in teeth and bones are due to a chemical disturbance unrelated to the parathyroid glands. This author believes that the appearance of osteosclerosis in both clinical and experimental chronic fluoride poisoning may throw some light on the etiology of idiopathic osteosclerotic diseases. Schour and Smith¹⁰ have concluded that fluorine probably exerts a direct local action on the enamel-forming cells, and that the observed changes in the enamel and dentine are not produced primarily by changes in blood calcium and phosphorus or by disturbances in the parathyroids. Phillips, Hart, and Bohstedt⁷ studied fluorosis in dairy cows, and showed that a fluorine intake in excess of 3 mg. per kilo of body weight greatly reduced milk production, that reproduction was unaffected, but that there was a delay in the appearance of estrus after parturition and a lower body weight in the newborn calves.

For the most part, interest in the effects of long-continued ingestion of small amounts of fluoride has centered in the changes produced in bones and teeth, especially the latter because the changes are more obvious, although they may not be the more serious. It has been shown by Wilson and DeEds¹⁴ that thyroid exerts a syner-

gistic action on fluorine toxicity, and DeEds, Wilson and Cutting³ have shown the same to be true of thyrotropic hormone. Not only is there a hormonal relationship to fluorine poisoning, but there may be other and far-reaching effects due to the fact that fluorine is a general protoplasmic and enzymatic poison. Phillips and Hart⁶ studied the effect of organic dietary constituents upon chronic fluorine poisoning in the rat and concluded that the mode of action of fluorine is systemic in character and is produced by a general inhibition of enzymic systems, and that fluorine may interfere with, or disturb, the actively metabolizing systems involving phosphoric acid esters.

The sample of dicalcium phosphate used in this investigation was obtained in 1937 and had a fluorine content of 2700 parts per million. Hence, an average daily dose of 60 grains (or 3.8 gm.) represents a fluorine intake 10 times the amount known to be injurious to teeth. Therefore, the fluorine content of dicalcium phosphate should not exceed a maximum of 0.02%, or 200 parts per million. No information is available regarding the fluorine content of dicalcium phosphate on the market at the present time (1941).

Summary. 1. The toxicity of fluorine present in dicalcium phosphate has been investigated, using the bleaching of rat incisor teeth as a criterion of injurious action.

2. The fluorine present in dicalcium phosphate has been shown to be as physiologically active as fluorine administered as sodium fluoride.

3. An average daily dose of 1 teaspoonful of dicalcium phosphate containing 0.27% fluorine represents a fluorine intake 10 times as great as the amount said to produce mottled enamel in at least some children.

The author is indebted to the Food and Drug Administration, Federal Security Agency, for data on the fluorine content of 16 samples of dicalcium phosphate prepared before July, 1939, by various American manufacturers. The fluorine content of these samples, expressed as parts per million ranged from 11 to 498, and 9 of the 16 samples ranged in value from 30 to 66.

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THE RESPIRATION IN MYASTHENIA GRAVIS.

BY DANIEL LASZLO, M.D.,

RESEARCH ASSISTANT FOR MORBID ANATOMY, MOUNT SINAI HOSPITAL, NEW YORK CITY

AND

F. C. REDLICH M.D.,

NEUROLOGICAL UNITS, HARVARD MEDICAL SCHOOL, BOSTON CITY HOSPITAL,
BOSTON, MASS.

IN the past few years our knowledge of the pathophysiology of myasthenia gravis and its treatment by prostigmine has been greatly increased by many publications, especially those of M. B. Walker,¹ Boothby,² Kennedy and Moersch,⁴ Viets and Schwab,⁸ and Minot, Dodd and Riven.⁶

Comparatively few observations have been made of the function of breathing in patients with myasthenia gravis, although the respiratory muscles are often involved in these subjects, giving rise to disturbing and occasionally alarming symptoms. K. Mendel⁵ commented on the roentgenologic evidences of respiratory changes in persons with myasthenia gravis. Albertoni¹ noted the presence of Cheyne-Stokes respiration in this condition, while Minski and Stokes⁷ used kymographic respiratory curves to demonstrate the beneficial effect of prostigmine. Gammon and Scheie³ studied the effect of prostigmine upon the height to which a mercury column could be blown. In contrast to other central or peripheral lesions studied so far, the authors found only in patients with myasthenia gravis a definite improvement. They advocate therefore the use of prostigmine as a diagnostic test for this condition.

We studied some aspects of the respiratory function in 5 subjects with classical myasthenia gravis. Two of these patients suffered from recurrent severe suffocative attacks characterized by extreme restlessness, a feeling of anxiety, pale cyanotic discoloration of the skin, rapid feeble pulse, fever, and labored breathing. The rapid shallow breathing during an attack was carried on predominantly by the accessory respiratory muscles with very little movement of the chest or diaphragm and was interrupted by a continuous dry hacking cough. Wheezing râles were present over the entire chest and numerous rhonchi were audible in the bases. This syndrome may be considered as an atelectatic pneumonia induced by the inefficient breathing apparatus.

We were interested in ascertaining the degree of disturbance in breathing in myasthenia gravis and in determining whether simple tests of the respiratory function could be used for gauging the severity of the disease. The following functions were studied in 5 patients with myasthenia gravis: 1, The vital capacity, its changes in relapses and during remissions induced by prostigmine. 2, The muscular and diaphragmatic movements as determined by

roentgenographic methods. 3. The degree of oxygenation of the arterial blood.

The vital capacity fluctuated widely in the same patient but was distinctly low in all 5 cases. In general, the more severe the myas-

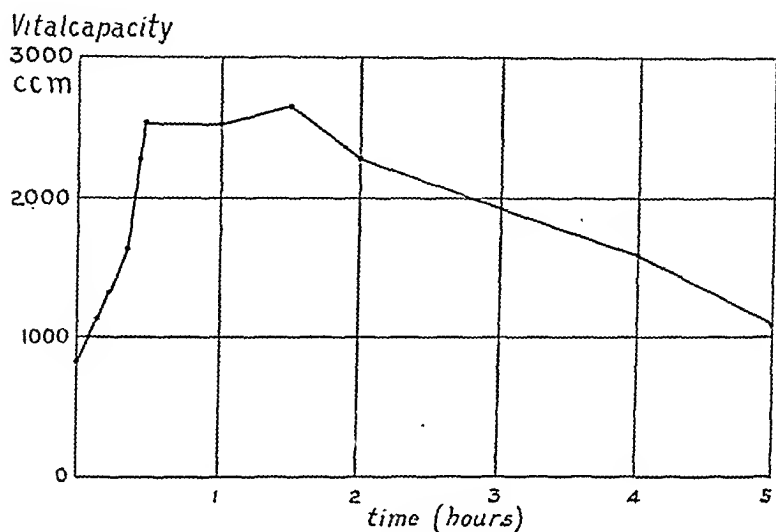


CHART 1.—Increase of vital capacity in myasthenia gravis after subcutaneous administration of 0.001 gm. prostigmine.

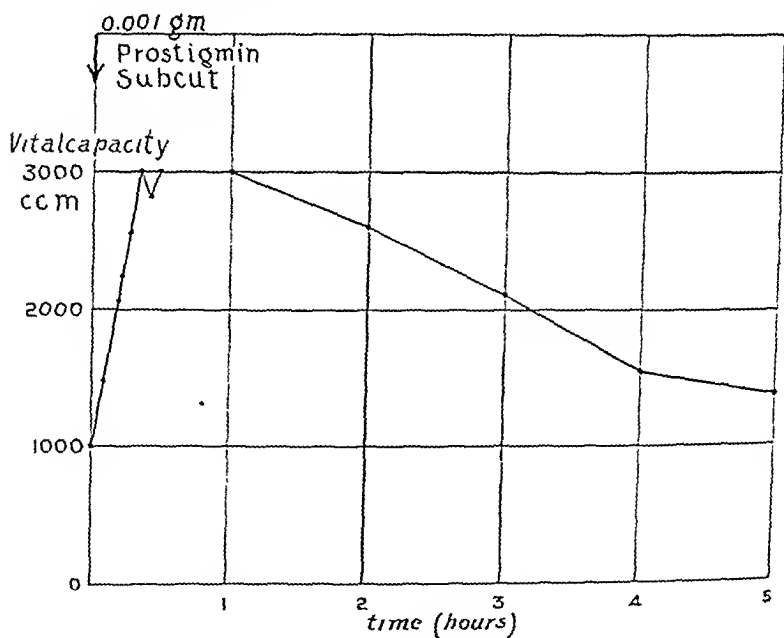


CHART 2.—Increase of vital capacity in myasthenia gravis after subcutaneous administration of 0.001 gm. prostigmine.

thenia the lower was the vital capacity. In the 2 severest cases exceptionally low values (400 to 500 cc.) were observed, while during the suffocative attacks the vital capacity could not be measured. Injection of prostigmine in these subjects was followed by a prompt rise in vital capacity, occurring simultaneously with the improvement in the patient's general condition. This reaction is illustrated graphically in Charts 1 and 2.

TABLE 1.—CORRELATION BETWEEN VITAL CAPACITY AND MUSCULAR FUNCTION FOLLOWING PROSTIGMINE.

Time (min.).	Vital capacity.	General condition.
Before prostigmine	1100	Dysarthric speech, lid lag, difficulty in swallowing, passive recumbent position, arms can be raised to 20-degree angle
<i>Injection of 0.5 Mg. Prostigmine Subcutaneously.</i>		
2	1400	Arms can be raised to 45-degree angle
6	1600	Can look up, speech unhindered, swallowing possible
8	1900	Arms can be raised to 90-degree angle, patient can get out of sitting position and walk several steps unsteadily
10	1900	No change
20	2000	Can hold arms outstretched for several minutes, walking improved
23	2300	Can stretch arms, and walking, speech, ocular movements and swallowing normal
30	2400	No change
60	2500	No change
90	1900	Fatigue after 20 steps; maximum arm raising to 45-degree angle, mild ptosis
120	1700	Ptosis unchanged; arm raising to 30-degree angle; has to stop after walking 5 steps
180	1500	Arm raising to 30-degree angle, walking and standing impossible
240	1400	Unchanged
300	1200	Speech, swallowing and eye movements as before injection; patient cannot rise from recumbent position

The improvement in the vital capacity as well as in the general condition may be noted within 10 minutes after the injection of prostigmine and may last several hours.

For some unknown reason the response to prostigmine varies in different individuals and in the same individual from time to time. It is important to note, however, that changes in the vital capacity paralleled closely the changes in other muscular functions. This correlation is illustrated in Table 1. It is typical of reactions which we have observed repeatedly in these patients following the administration of prostigmine.

This parallelism was observed in the spontaneous remissions which frequently occur in this disease, as well as in those induced by prostigmine, clinical improvement being reflected in the increase in the values for the vital capacity. On the other hand, in several instances in which no marked clinical improvement followed the injection of prostigmine no appreciable change in vital capacity was detected.

The spirometric method may be used to demonstrate the efficacy of various therapeutic measures in myasthenia gravis. We found, for instance, that caffeine, strychnine, ephedrine, veratrine and inhalation of mixtures of CO_2 and O_2 had no distinct influence on the symptoms and signs in myasthenic patients who responded promptly to prostigmine.

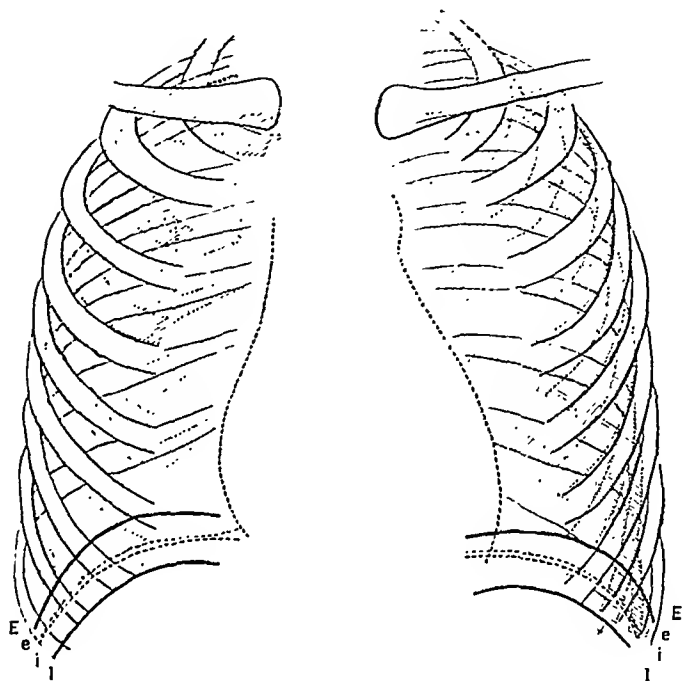


FIG. 1.—Myasthenia gravis. The diaphragm level on normal (.....i) and forced (——I) inspiration and normal (.....e) and forced (——E) expiration before prostigmine.

Roentgen ray and fluoroscopic observations were made by Dr. F. Fleischner on patients with myasthenia gravis in various stages and during periods of remission induced by prostigmine. When the vital capacity was diminished, the most striking abnormalities noted were: 1, Reduced motility of the diaphragm, amounting in severe cases almost to paralysis. 2, Elevation of the ribs and thoracic lordosis. 3, In severest cases signs of atelectasis. The prompt restoration to normal diaphragmatic and thoracic motion following the administration of prostigmine may be strikingly observed fluoroscopically. This reaction is illustrated in Figures 1 and 2.

The marked reduction in the breathing surface led us to investigate the question of arterial oxygen saturation. Blood was drawn in paraffined vessels from the brachial or femoral artery and analyzed for its oxygen content and oxygen capacity, using the method of Van Slyke. The results in 3 experiments are shown in Table 2.

It may be seen that despite the extreme reductions in vital capacity there is little or no diminution in the oxygen content or saturation. The hyperpnea, no doubt, compensates in part for the inefficient muscular action. The absence of hypoxemia despite the low vital capacity may be contrasted to the conditions which we observe in pulmonary edema or pneumonosis where arterial hypoxemia may

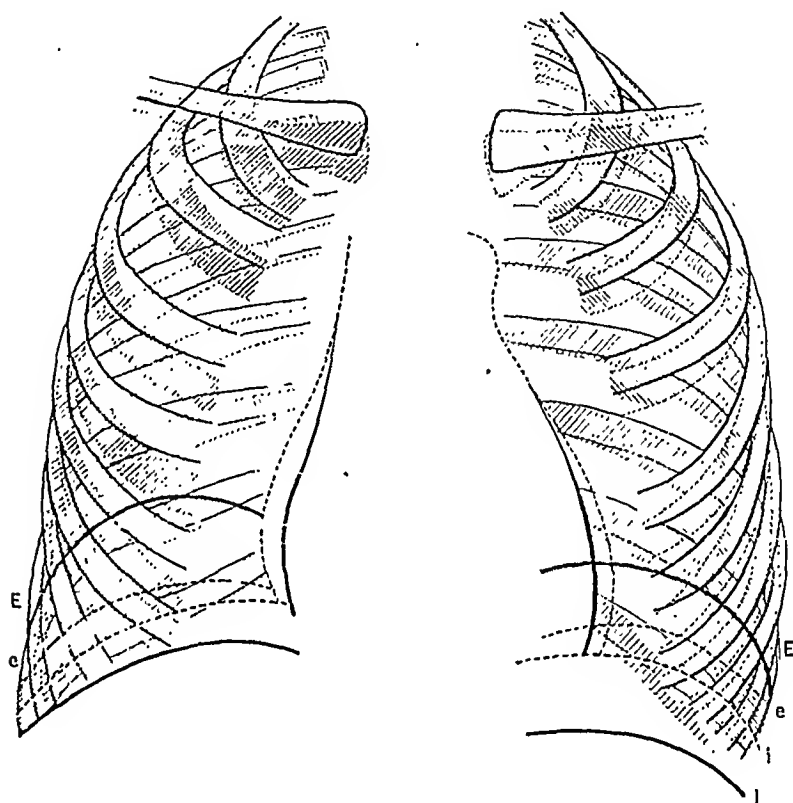


FIG. 2.—After subcutaneous prostigmine administration.

TABLE 2.—ARTERIAL O₂ CONTENT AND SATURATION, VITAL CAPACITY BEFORE AND AFTER PROSTIGMINE.

Patient.	O ₂ content (vol. %).		O ₂ saturation in % of total capacity.		Vital capacity (cc.).	
	Before Prostigmine.	After	Before Prostigmine.	After	Before Prostigmine.	After
St. K. . . .	15.74	16.79	95	99	600	2200
Fr. St. . . .	16.95	17.72	92	99	1000	2600
M. D. . . .	22.64	22.64	99	99	1000	2000

be present associated with vital capacities considerably higher than those recorded above. The arterial anoxemia in the latter is presumably due to difficulties in gas diffusion through the pulmonary alveoli. The absence of this barrier in our patients may serve to explain the apparently normal aëration of the blood in the lungs.

Measurement of the vital capacity is simple, objective and directed to a vital bodily function. It is recommended as a supple-

ment to the functional tests used in patients with myasthenia gravis to determine the severity of the disease and the efficacy of therapeutic agents.

Summary. Certain aspects of respiratory functions were studied in patients with myasthenia gravis. The vital capacity is greatly reduced due to inefficiency of the diaphragm and auxiliary muscles concerned in breathing. Changes in vital capacity parallel closely alterations in the general state. It may be used as a reliable measure of the severity of the disease and the efficacy of therapeutic procedures. Despite extreme reduction in vital capacity there is no apparent interference with oxygenation of blood in the lungs.

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THE INTESTINE AND CHRONIC ARTHRITIS.*

BY ANTHONY BASSLER, M.D., F.A.C.P., LL.D.,

CONSULTING GASTRO-ENTEROLOGIST TO ST. VINCENT'S, MISERICORDIA, NEW ROCHELLE,
ST. JOHN'S, ST. AGNES, JEWISH MEMORIAL AND CHRIST'S HOSPITALS,
NEW YORK, N. Y.

AURELIANUS, in the fourth century A.D., considered an arthritis as of gastro-intestinal origin with a hereditary predisposition. Paul of Aegina regarded the intestinal tract with its disorders as contributing to both gout and arthritis. Popoff, in 1887, experimentally produced arthritis with streptococci, which has been confirmed by others. Burbank and Hadjopoulos, with an antigen from streptococci obtained from the blood and upper respiratory sources studied various infective foci remote from the intestinal tract. It has not been emphasized, however, that intestinal organisms might by their presence in the blood stream be a cause of joint disturbance and by way of continued reinfection assail the local and general immunity production forces.

There is no totally distinctive change in the generally recognized two types of chronic arthritis, which are usually recognized as having a wide overlap. The thickening and round cell proliferation of the synovial membrane, granulation over the synovia, adhesions with increase of fibrous tissue, involvement of the periarticular

* Read before the Mid-Hudson Chapter of the National Gastroenterological Association, January 26, 1941; Lackawanna County Medical Society, Scranton, Penna., April 15, 1941; New Rochelle Medical Society, April 14, 1941; and the New York Ruptured and Crippled Hospital, April 21, 1941.

tissues, ankylosis and the cementing together of joints are seen in both types. The pathologic pictures in spondylitis is similar to that of joints and bones elsewhere in the body. Although the cases have similar changes, the predominance of one or other type warrants the use of the terms atrophic or hypertrophic. There is much about them that suggests some type of an infection as an important etiologic factor.

Not much credence has been placed in the value of skin reactions or allergic tests to bacteria to suggest the infective unit, and the same may be said about the presence of agglutinins and precipitins, to streptococci particularly. Paul⁴ points to the concept of focal infection not playing a part in the continuation of the disease although the so-called "eradication of foci of infection" may be of benefit in the early stages of rheumatoid arthritis. Others believe that a focal infection may be a "precipitating" factor but that it is not the fundamental cause of the continuation of the disorder. This is suggested in that the removal of focal infections does not benefit the average chronic case, and if so, mostly in the indirect way of improving the general state of health. There is believed to be insufficient evidence that any of the organisms which may be demonstrated in a focal infection actually causes arthritis. Burbank states that he has demonstrated streptococci in the canaliculi of the cancellous tissue of joints; but in the vast majority of the cases this condition is not present and almost never late in the disease. There have been suggestions that it is a systemic disease in origin. For instance, arthritis may ensue in hyperthyroidism, the menopause, after coronary thrombosis, exposure to damp and cold, nervous shock, psoriasis, ulcerative colitis. This, however, does not eliminate the intestine as a cause.

We may agree that there is some clinical evidence that points to an initial infection starting arthritis, and, accepting the intestinal canal as one of the sources of this infection, that slow additions of bacteria, even if they do not successively lodge in the joints, may continue it. We have three substantiations for this assumption: 1, it is proven that bacteria pass through the walls of the intestine; 2, that even in clean cases the peritoneal cavity may contain intestinal bacteria; and 3, that intestinal bacteria may be found in the general blood stream. We would deal, then, with organisms in the digestive canal which gain the circulation and unless they are controlled in the intestinal tract, the results from most treatments would be limited. The process then would be an infection of the blood stream from the bowel and the lodgment of the bacteria in the canaliculi of the cancellous tissue adjacent to joint surfaces (where they are the smallest in the body) and the periarticular tissues, their destruction by local immunities causing a reactive change, and the local processes continuing in allergic ways by further blood stream infection or absorbed specific toxins from the bowel.

The high incidence of intestinal bacteria in the blood of one vein tap in non-arthritic as well as arthritic persons (5% to 8%),^{1c,2} the remissive character of the disease and the benefits from intestinal treatments suggest this factor. The fact that the body often has to contend with intestinal bacteria in the blood stream and that only about 2% or 3% of the population in the United States becomes a victim of chronic arthritis, suggests that some people are more lucky than others in their immunity makeup, that there may be an hereditary or biologic resistance to an infection, or that many of the organisms are not joint selective in nature. Such assumptions are more reasonable to entertain than that there is some form of a "virus" as its fundamental cause, that rheumatic arthritis "is a systemic disease" of some mysterious nature, or that it is totally "metabolic" in cause. For the latter we have no bases of reasoning such as we have in the initial joint infection with the development of an allergy to the bacteria present in chronic arthritis.

In 1920^b attention was drawn to the colon in connection with chronic arthritis. Thirty-four cases of typical polyarthritis were described, in which but one improved noticeably from the removal of a focal infection above the clavicle, and 10 showed no evidence of focal infections. The clinical findings and methods of handling were described, and the results in the joints by the handling of a chronic biotoxigenic intestinal condition presented. Of these 44 cases, marked improvement was observed in 21, moderate in 19, and none in 4. Attention was drawn to arthritis and the colon in connection with type diets and infections with *C. welchii*, Gram-positive single and double cocci, *B. putrificum*, and pathogenic types of *B. coli*, staphylococci and streptococci. With apologies for quoting myself, the following was presented, "There is good reason to believe that in the early course of this disorder if attention is given to the colon, as well as to other focal infections, many would be saved a fate of chronic joint deformity and invalidism." But in the last 20 years the significance of streptococci as an etiologic factor in chronic arthritis has received pointed attention, and the writer now desires to modify his original conception of a chronic biotoxigenic intestinal state causing the disorder in a catabolic way, and agree to the bacteria themselves as probably the more important factor.

The writer^{1d} drew attention to several types and strains of streptococci recoverable from the intestinal canal, those of the fecalis, mitis, equinus and hemolyticus types being most frequently found. Because of the variation ability of all streptococci when studied by cultural methods, sharp genus differentiation of the various types leaves doubts about the hemolytic, non-hemolytic and green-producing types being definite separate forms. The distinct blood-laking types (pyogenes, hemolyticus, hemolyticus I and II) are conspicuous in this mutation ability, and this no doubt is true with all streptococci. Of the various types (of which there are some 35

or more), all streptococci are hemolytic to some degree. The question here of hemolytic power is largely one of degrees, this commonly changing in what appears to be the same strain. There is evidence, however, that streptococci are common denizens of the intestinal canal in apparently healthy persons and that distinct high hemolytic forms are met with in about 7% of normal persons, and that when there is disease and disorder of function in the bowel they are met with more often. In 50 cases of ulcerative colitis, for instance, high hemolytic streptococci were met with in 42 cases, and the non-hemolytic and viridans in all. A factor of importance in the presence of pathogenic streptococci is that they are more often met with when certain other bacteria are present. These particularly are the organisms of the Eberthella, Salmonella, Shigella and Escherichia groups to which others to be mentioned can be included. In clinical medicine these symbioses appear to be an important factor in infections. Not only do certain organisms multiply freely in the presence of others, but also there is suggestion that added virulences and toxicities are acquired by the combination, such as is present in pulmonary tuberculosis for instance. In no part of all infections is this so important as it is with organisms in the intestinal canal. The more definite the incidence of a mixed infection, very probably the more definite is the etiologic significance of the streptococci. To appreciate the significance of streptococci in the bowel, it is necessary to study the association of these other organisms, because apparently streptococci in significant numbers do not continue in the intestinal canal without an associated infection to assist them. It is possible that non-streptococcic organisms recoverable from the blood stream would also have significance as enhancing and allergic factors in chronic arthritis. Most often the organisms recovered from the blood stream are streptococcic in origin, although morphologically and culturally they may not appear to be unless they are studied by different medias and after passing through several subcultures. A student of intestinal bacteriology can look with doubt upon any specific streptococcus causing rheumatoid arthritis, such as the Hastings-Bedell strain and that recently suggested by Cecil, Nicholls and Stainsby.³ Burbank appears to be nearer correct when describing the ignavus, fecalis, viridans, infrequens, mitis, salivarius, equinus and subacidus, all of which are common denizens of the human intestinal canal and all of which are mutable. It is reasonable to believe that a streptococcus met with in the joints of chronic arthritis could have been one of the well-known more innocent strains initially and by mutation acquire a virulent factor and even different culturable abilities and staining characteristics. Often in blood cultures one seems to be dealing with a bacillus which on cultural observation ends up as a coccus. Even in the Gram-negative organisms mutation-like changes appear to be common.

A group of cases of chronic arthritis were studied and treated along biologic ways. These patients were placed upon a test diet (p. 94),¹ casual stool specimens being considered unsuitable. This diet was maintained for 72 hours and a purged specimen used for culture studies. The stool first was examined for general character, reaction, food detritus, ova, and so on, and note made of the conspicuous types of microorganisms present. Specimens were then inoculated into different medias, more particularly as follows: For the streptococci, beef-heart infusion and with agar, beef blood and brain-dextrose broth; for the Eberthella, Salmonella and Shigella organisms, the MacConkey, bismuth-sulphate agar, tetrathionate broth, Ligler iron-agar or Krumwiede triple sugar agar were employed; for the coloniform organisms, egg meat mediums, endo, MacConkey's and Krumwiede media. A separate set of observa-

TABLE 1.—ANALYSIS OF 331 CASES OF ARTHRITIS (GENERAL GROUP).

Description.	No.	Acute.	Chronic.	Improved.		
				Greatly.	Mod.	Not.
Cases eliminated for various reasons . . .	37					
Cases in which a positive focal infection existed (other than intestinal) and initially treated as such* . . .	109	11	98	24	19	66
Cases in which gonorrheal infections were possible; these are included in the focal infection Group 2† . . .	6	..	6			
Cases in which the arthritis was considered as due to gout and treated as such‡ . . .	21	8	13	14	1	6
Endocrine instances treated first by estrogens and other glandular products§ . . .	92	7	85	16	18	58
Trauma and exposure considered important; treated by rest, splints, etc.§ . . .	9	..	9	2	..	7
Positive Wassermann and Kahn cases; treated for syphilis for 4 months§ . . .	5	2	1	2
Considered as gastro-intestinal initially . . .	58					

* Of the acute cases they all improved satisfactorily. All of the moderate and non-improvement cases were treated intestinally subsequently.

† These were cases in which there had been a history or a possibility of this infection (eroded cervix), tender or swollen Fallopian tubes, pus cells in prostate strippings. Two were added to the intestinal group subsequently.

‡ The moderate and no improvement cases were added to the intestinal group subsequently.

§ The non-improved cases were added to the intestinal group subsequently.

tions for 10 days were made with lytic tubes containing 2% dextrose bouillon to study the incidence of phage action and to note the most persistent types or forms, those lysing in the first few days being regarded as not important. This method is also useful for subculture identifications. Other than the streptococci and staphylococci, the rest of the Gram-positive organisms (the strict anaërobic types) did not get much attention, as they were regarded as insignificant in a pathogenic sense in these cases. Three blood cultures apiece were made routinely in 100 cases, with several media. These were positive in 17% of the instances. As this was 8% on one vein tap and 12% on 2 taps, and 17% on 3 taps, a group of 25 cases of chronic arthritis was tapped weekly for 10 times and in these there were 11 positive, practically 44%. It seems reasonable to assume that if more vein taps were made a still higher percentage of positives would be noted, even accepting that our cultural methods are not

as satisfactory as could be desired. Ten vein taps were made on each of 25 healthy individuals for a comparison, here 12% being positive. Apparently in chronic arthritis the incidence of positive blood cultures is higher than in healthy cases. It would be interesting to know what the incidence of positive blood cultures would be in chronic disease other than chronic arthritis. Even then, however, the question of joint selectivity of bacteria and allergy could not be judged.

TABLE 2.—TOTAL OF 202 CASES TREATED GASTRO-INTESTINALLY (94 MALES, 108 FEMALES).

Description.	No.	Improved.		
		Greatly.	Mod.	Not.
Secondary biotoxigenic states due to various gastro-intestinal conditions other than primary biotoxigenic intestinal states and treated as such initially*	51	36	8	7
Considered as probably straight streptococci infections and treated as such with fecal streptococci as vaccines†	21	12	7	2
Primary biotoxigenic intestinal states of mixed infections treated as such	181	124	33	24

* The moderate and non-improvement cases are included in the primary biotoxigenic group.

† The 2 not improved were added to the biotoxigenic group.

According to the bacterial findings and significances, biologic treatment was set up, in as simple form as possible to be practical. Briefly they were as follows:

1. *Rectal Instillations.* On the bases that antagonisms existed between the strains of the *B. communior*, *B. aërogenes* and *B. acidilactici* of *Bacilli coli* (Dunham's classification) and the other strains of *Escherichia coli* and forms of pyogenic and zymogenic organisms^{1a} (in which the *Salmonella* and *Eberthella* are included), bi-weekly rectal injections were employed in the cases all the way through the treatment. Fifteen cubic centimeters of a 24-hour growth in 2% dextrose bouillon of each (making totally about 15 trillion viable organisms) were made up to 100 cc. by the addition of a 1% dextrose solution, after which the patient rested on the left side for 15 minutes. In about half of the cases an insignificant drop in the leukocyte count of a fifth to a third was noticed at about 8 hours after the first few culture instillations. After about 2 months of treatment a subjective sense of fatigue may be complained of by the patient, and toward the end of treatment a few will present a slight amount of disorientation. This may be controlled by a moderate dose of aspirin after which the instillations should be stopped. The rule was that when the injected strains of *B. coli* continued growing in the colon, advantage was taken of the patient's selectivity to these organisms and cultures were made directly from the patient's stools and used instead of stock strains. This apparently is a distinct advantage.

2. *Oral Phages.* In all of the well-advanced and established cases, and when distinct benefit has not been brought about in a few weeks' time, a phage type of mouth administration was also employed. According to the observation made in lytic observa-

tions,* the time was noted when further phage treatment did not take place from day to day. The then persisting and resisting types of organisms were inoculated into 500 cc. of 2% dextrose bouillon, grown for 48 hours and sterilized by filtration through candle filters. Usually several filtrations were necessary for sterilization. Various chemicals were used to render this material safe from further bacterial growth, but none were so successful as care in the initial candle sterilization and very cold ice-boxing as a preservative. This product should only be used when crystal clear, and when it becomes the slightest bit foggy, it must be discarded. This phage product was taken each morning by mouth in 5 to 10 cc. quantities before breakfast, preceded and followed by a tablespoonful of olive oil. When distinct clinical benefit had been brought about, this item of treatment was modified and discontinued. It is impossible to state how this produces additional benefit, but that it is an item of considerable importance there is no question.

3. *Vaccines*. If the blood cultures showed the presence of Gram-positive cocci and at times if the stool specimens of lytic tubes suggested their prominence and persistence, concentrated vaccines were made and used intradermally and subcutaneously. These were not sterilized by heat. The washings from the surface of agar tubes (using for the purpose a small amount of the following mentioned merthiolate solution) were made up to about 5 times the volume with a 1 to 5000 merthiolate solution made up by the addition of sodium chloride to a physiologic salt solution. Such a mixture is bacterially sterile in 48 hours.

No effort was made to count the bacteria, local reactions being used to suggest the dose. The vaccine was started with 1 minim given with a tuberculin syringe and a very fine needle. According to the local reaction, the dosages were slowly increased usually at about 1 minim at a time and given twice a week. The dosages were kept short of pronounced reactions, small doses over longer lengths of time being regarded as a better plan. These were usually given midway between the rectal instillations although often were administered on the same day. In tight skins when the quantity given was greater than could be injected between the layers of the skin, the remainder of the dose was injected subcutaneously. There is also no way to estimate this biologic item of treatment; at times it seemed worthwhile but in many of the cases not so. The rectal and mouth types of treatments were depended upon more. In the

* Two ordinary test tubes were employed, each containing 15 cc. of 2% dextrose bouillon and inoculated with a streak on the side wall of the tube using a straight inoculating wire which had been plunged in feces. Tube 1 is the aerobic tube using the media as such. The contents of Tube 2 is boiled actively for a few minutes to drive out the largest percentage of air (oxygen) which the media has acquired on standing. The contents are rapidly cooled, inoculated as in Tube 1 and then covered with toluol or mineral oil. The latter is a fair type of anaerobic procedure, simple and found to be practical enough for this work.

cases of staphylococci and organisms other than the streptococci, the vaccines seemingly were more efficacious but accurate observations on this point are not possible to elucidate with sufficient degrees of accuracy. It is well known that streptococcic vaccines are notably ineffective for immunity production and it was deemed that the streptococci were not the total infection factor in chronic arthritis.

The suggestion from these cases was definite that when the symbiotic organisms were controlled, the streptococci in both the intestine and the blood stream was also controlled.

A purged specimen of stool was checked each month and the biologic treatments were modified or maintained according to the suggestion of the findings at these examinations and the clinical improvement. This stool checking was done for 4 or 5 months, after which the stool specimens are examined for 6 months after the discontinuance of biologic treatments. If the case was of the marked improvement type and then became worse again (chronic arthritis is a remissive disorder), a purged stool specimen (on the diet as initially) was again examined and the biologic set-up of treatment established according to the findings. There were usually several shifts or modifications in the biologic handling in the majority of cases.

The diets fundamentally followed the rule indicated in chronic biotoxic intestinal conditions. In the putrefactive or alkaline form, high carbohydrates and hydrocarbons and sharply limited proteins of readily digested forms were given; in the fermentation or acid form, high protein diets with limited carbohydrates (5%) and a severe control of hydrocarbons. Effort was made to control the total intake of food in those above normal weight (Medico-Actuarial Mortality Investigation, 1912), and additional foods urged in supplemental meals in those definitely below these standards. This was not followed too strictly, because in the obese debility may ensue, and in the underweight the digestion often became embarrassed. Calcium in any form was regarded as contraindicated; foods as low in calcium content as possible were selected. No attempt was made to benefit an anemia with iron-bearing foods but by liver and iron therapy. The bowels were moved by lactose, dextrins, food roughages, and agar, but mineral oil preparations and the salines were not employed. Cascara, low simple enemas and occasional small doses of calomel were employed. Colonic irrigations were not used, and where definite clinical food allergies existed these foods were avoided.

Treatment was influenced by the pathogenic bacterial findings, and more particularly directed toward influencing symbiotic types rather than only definite strains. Of these microorganisms, in addition to the Eberthella, Salmonella, Shigella and Escherichia, *Strep. alcaligenes*, Gram-positive enterococci (both single and double) and *Etherobacilli Prodigiosus* were of interest. It was assumed that

the last named, though less than Eberthella, Salmonella, Shigella and Escherichia, might act as symbiosing and enhancing factors with streptococci, but no special attention was paid to them. On the whole, this symbiosing factor on the part of the bacteria with streptococci is impossible to estimate accurately. All one can do is to assume in the individual case that such a possibility exists and that their presence may act as enhancing, conversion or mutation factors to the streptococcal infection (the *Strep. fecalis*, for instance) thereby rendering these more innocent forms of streptococci important as infecting agents. It is reasonable to assume that the average person should develop immunities against low-grade infections better by natural means than could be accomplished by therapeutic immunity procedures. Yet clinical medicine suggests this is not always accomplished, and that biologic measures can produce active immunities. While a "gang member" in arthritis is in all probability some form of streptococci, they would not be important without the supporting and enhancing bacteria that are associated with them. In this sense the streptococci are only part of an associated infection and perhaps even only that of a secondary invader.

Another point of importance is that various conditions in the digestive canal can bring these bacterio-toxic factors about in a secondary way. Pemberton and others have drawn attention to ptosis, angulation, gall-bladder disease, constipation, and so on, being significant in connection with the subject of chronic arthritis. Here, however, we deal with gastro-intestinal or medical conditions in which the content of streptococci and even the symbiotic infections are possible of being corrected by attention to the disorder resident in the digestive tract. Especially is this observed where normal transit through the colon, or incomplete bowel evacuations exist. While ameliorating in the majority of instances, the correction of these did not always produce marked enough amelioration of the chronic arthritis, although at times it was striking. It thus is obvious that the treatment of these more strictly gastro-enterologic states would be in order initially in every instance of chronic arthritis. The cases treated biologically were all primary in type.

Twenty cases were treated by the various sulphanilamide preparations, 6 with moderate improvements lasting a short time. Apparently a few cases of arthritis will improve on this therapy possibly by controlling the streptococcal systemic factor from the intestine for a time. No effect that is appreciable from laboratory studies beyond a bacteriostatic one can be demonstrated by sulfanilamide on the streptococci or other bacteria resident in the bowel, although it is possible that such may take place to slight and temporary degrees. No observations were made on the control of systemic infections by sulfanilamide drugs in the blood stream. Up to the present it has been proven that they are practically ineffective in ulcerative endocarditis in rendering the blood stream negative.

Sulfaguanidine was not used. The experience with these drugs suggested that one cannot deduct as to which one of the preparations would be best to employ. When benefit takes place from them, it seems to be about the same, whether one uses sulfanilamide, sulfapyridine or sulfathiazole. It was slightly suggested that sulfanilamide seemed to be the better form in *C. welchii*, hemolytic and the green streptococci, and sulfathiazole in the inimical form of *E. coli*, aërogenes, pyocyaneous and streptococcus infections of the bowel.

The ordinarily employed different vitamin preparations were not encouraging in results although vitamins were more or less employed in all the cases. Five cases of chronic arthritis were intensively treated with large doses of vitamin D (Estron) without benefit. The most benefit seemed to come from the various B complex preparations providing the doses are ample, kept up for months, and especially if the preparation had a laxative effect on the patient.

The writer desires to report 337 instances of chronic arthritis observed by him from 1923 to the present. For the purpose of eliminating the generally recognized factors were treated for various lengths of time, and those that were unimproved were examined and treated by biotoxic measures.

Summary and Conclusions. Intestinal organisms are more or less frequently passing into the general blood stream, probably by way of the peritoneal lymphatics. The human intestinal canal, even in apparent health, contains many forms of streptococci, potentially pathogenic in the circulation. Under conditions of symbiosis with certain other organisms in the intestine, these streptococci can become pathogenic. Organisms may appear in the blood stream in unusual types when they are still the original forms. Gaining the circulation, streptococci may lodge in the cancellous tissue of the bone under the joint bone or surfaces and in the periarticular and fascial structures causing an initial infection. These tissues then may become sensitized to them, and as more streptococci, and perhaps some of the mixed infection types, are added to the circulation, a remissive, progressive change in the joints or bones ensues. These primary and reinfective factors from the intestine have not received the attention they deserve in the subject of chronic arthritis. While the use of streptococci vaccines may be of value, they are not efficient in controlling the infection in the intestine. In most instances attack on the associated infections by biologic and dietetic means controls the streptococcic infection, this being important on the parasitic character of the streptococci within the bowel as well as those that gain the blood stream.

A method of biologic and dietetic treatment for chronic arthritis is suggested. The results of handling 337 cases of chronic arthritis, 205 of which, by gastro-intestinal treatments, are presented. Of the latter, about 17% having treatment for the various well-known

digestive disorders causing secondary biotoxic states showed improvement. In 181 cases of primary biotoxic intestinal conditions practically 68.5% showed marked improvements in reduction of swelling, usefulness of joints and control of remissions, and about 26.5% more were distinctly improved, there being about 9.2% of failures, these latter being old cases with much deformity.

A reasonable conclusion from these results is, that, while other causes than intestinal have importance in chronic arthritis, significant etiologic and therapeutic factors are contained in the digestive tract, and of these, infections of intestinal origin comprise an important group.

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THE AMOUNT OF IODINE IN THE BLOOD AND URINE IN PATIENTS WITH DIABETES INSIPIDUS.

BY HARRY BLOTNER, M.D.

ASSOCIATE IN MEDICINE, PETER BENT BRIGHAM HOSPITAL, BOSTON, MASS.

(From the Medical Clinic of the Peter Bent Brigham Hospital.)

RECENTLY, Blotner and Cutler² reported certain observations on the effect of total thyroidectomy in 3 patients with diabetes insipidus who were observed for 5 years following operation. Total thyroidectomy relieved the excessive urinary excretion of the diabetes insipidus in 2 cases, while no effect was noted in the other case. However, in the latter case it was felt the patient had accessory thyroid tissue because of her normal metabolism and lack of signs and symptoms of myxedema. The administration of thyroid extract reestablished the polyuria and polydipsia in the 2 cases. Histologic studies of the thyroid gland in 2 of the cases indicated a small degree of hyperactivity. The above observations indicated that the thyroid gland played some rôle in the physiologic aspects of diabetes insipidus.

Since there appeared to be a relationship between thyroid activity and water balance in patients with diabetes insipidus, it seemed reasonable that this association could be more firmly established by observing the level of iodine in the blood and the excretion of iodine in the urine in a group of patients with diabetes insipidus. This paper deals with the results of the blood and urine iodine studies in 15 patients with diabetes insipidus.

Iodine is a normal constituent of human blood and urine. The values for the concentration of iodine in the blood vary somewhat

according to the method used. Nevertheless, in adhering to a standard procedure for determining iodine, results can be obtained which are relative one to another. Perkin and Lahey^{12b} have used an open combustion method as described by Perkin^{9b} in 25,000 analyses of blood iodine and found it to be satisfactory for clinical and research purposes. In persons without clinical evidence of thyrotoxicosis, they found that the average or mean level of iodine in the blood was 6.8 micrograms per 100 gm. with no significant variations attributable to age, sex or season. Curtis and Puppel^{3a} found that the normal person excreted in the 24-hour daily urine from .007 to .196 mg. of iodine or an average of .051 mg. and that there did not appear to be any relation between the amount of iodine in the urine and the volume of urine excreted. In the Boston district, Perkin found the daily urine excretion of iodine to range from .060 to .140 mg. with mean values of .090 to .110 mg. These values, however, may be influenced by the daily regimen.

There have been reported minor physiologic variations of the blood iodine level during the menstrual cycle,¹⁵ during pregnancy,⁷ seasonal variations^{4,8} and during exercise.⁶ These variations in the blood iodine level may or may not extend beyond the normal range for the method used. Elevation of blood iodine has been observed in patients with diseases of the liver and of the biliary passages,¹⁰ in leukemia⁴ and in the early stages of acromegaly.^{12b} However, the greatest variation from the normal appears in patients with hyperthyroidism. In this disease there usually occurs a considerable increase in the blood iodine level and a marked increase in the excretion of iodine in the urine. In hyperthyroidism, Perkin and Lahey^{12b} found that the average and mean values for blood iodine were 15.5 and 11 micrograms per 100 gm., respectively. These same workers^{12c} found the urinary iodine excretion of these patients to average .110 to .225 mg. per 24 hours with a maximum of .410 mg. In the urine of cases with hyperthyroidism, Curtis and Puppel^{3b} found a daily excretion of iodine ranging from .013 to .954 mg. with averages ranging from .030 to .595 mg.

Plan of Investigation. The work reported here was carried on according to the following methods. The iodine in the blood and urine was determined during and after a course of pituitrin therapy in a group of cases with diabetes insipidus. In the cases studied during the period of treatment with pituitrin, 1 cc. of obstetric pituitrin was taken three or four times a day intranasally or subcutaneously for from 1 to 10 weeks when the polydipsia and polyuria were well controlled before the tests were made. When the tests were made after pituitrin was omitted, a period of from one week or more elapsed after the discontinuance of pituitrin therapy, at which time the patients were drinking and passing huge volumes of fluid. The concentration of the total iodine in the blood was studied in some specimens taken before breakfast, in others, during the day. The determinations of the total blood iodine were made in duplicate, using 20 cc. samples of venous blood according to the method described by Perkin.^{9b} In addition, the organic and inorganic iodine fractions in the blood were determined in 11 of

the cases. The tests for iodine in the urine were made on 24-hour samples of urine obtained immediately either before or after the blood was obtained. The patients were instructed to follow their usual diet and the specimens were not taken when they had a sea fish meal which might reflect an increased amount of iodine in the blood and urine. One patient was observed in the hospital for 20 days when the fasting blood iodine and the 24-hour excretion of iodine in the urine were determined daily during periods with and without pituitrin injection.

Iodine tolerance tests were observed in 3 cases with and without pituitrin therapy. At least 4 weeks elapsed between tests. A standard dose of .6 cc. of compound solution of iodine (Lugol's solution) U. S. P. in a glass of milk was employed. The concentration of the blood iodine was determined in specimens taken during fasting and at intervals of 30, 60, 90 and 150 minutes after the ingestion of the iodine. The total amount of iodine was determined in the urine excreted during the 24 hours following the ingestion of the iodine in one case.

The total amount of iodine was determined in the thyroid glands of 2 thyroidectomized patients with diabetes insipidus and the results were compared with those obtained in 2 normal thyroid glands which were removed for the treatment of heart failure without hyperthyroidism.

Clinical Material. The group studied comprised 10 males and 5 females with diabetes insipidus who had the disease for a number of years. Their ages ranged from 11 years to 69 years, although the majority were between 20 and 30 years old. Their weights were about normal or somewhat below normal for their height, age and sex, but one patient was obese, weighing 205 pounds. The criteria for the diagnosis of diabetes insipidus were a persistent daily fluid intake and output of about 8 to 14 liters for years, which were reduced to normal following the intranasal or intramuscular administration of pituitrin. The disease was of idiopathic origin in 12 cases, of postencephalitic origin in 2 cases and due to a pineal tumor in one case. Two cases were relieved of their polyuria and polydipsia by total thyroidectomy about 4 years before the iodine tests were made. The various laboratory data were not remarkable except that the fasting blood cholesterol was elevated in some cases, not merely in the thyroidectomized patients, and usually showed a marked rise after a fat meal.¹ The basal metabolism ranged from +8 to -18%. In the 2 thyroidectomized patients, the basal metabolism was about -25%.

Results. The results of the total blood iodine level and of the total iodine excretion in the 24-hour daily urine in 12 cases of idiopathic origin are given in Table 1. These findings show that when no pituitrin was administered, the blood iodine was usually at a low normal level, although in one specimen it was elevated, being 12.6 micrograms per 100 cc. The average was 5.5 micrograms per 100 cc. In comparison, the average or mean blood iodine in normal people was 6.8 micrograms per 100 cc. with a range of from 3 to 10 micrograms with the method used.

The 24-hour urine showed varying amounts of iodine and in most instances, the iodine excretion was markedly increased. The average 24-hour urine iodine was .339 mg. and the average daily urine volume was approximately 10 liters.

When pituitrin was administered, the results were opposite to those when no pituitrin was given. In this instance, the blood iodine level was increased in most cases, the average being 9.8 micrograms

per 100 cc. The 24-hour urine excretion of iodine decreased considerably, the average being .177 mg. and the average daily urine volume was approximately 3 liters. A summary of these results is given in Table 2.

TABLE 1.—TOTAL IODINE IN THE BLOOD AND URINE OF 12 PATIENTS WITH DIABETES INSIPIDUS.

Case No.	<i>No pituitrin.</i>			<i>On pituitrin.</i>		
	Blood iodine, meg. per 100 cc.	24-hour urine, iodine, mg.	24-hour urine, volume, cc.	Blood iodine, meg. per 100 cc.	24-hour urine, iodine, mg.	24-hour urine, volume, cc.
1 . . .	3.0	.318	10,630	4.3	.079	960
2 . . .	5.6	.201	7,440	17.0	.125	2120
	3.6	.217	10,320			
3 . . .	7.0	.208	4,900	9.2	.143	1350
	6.7	.108	6,500	12.0	.078	1400
4 . . .	12.6	4.2		
	8.0	.936	9,360	6.8	.173	3840
5 . . .	3.2	.345	11,520	17.8	.127	5760
		.028	9,450	6.5	.168	2400
	7.8	.147	10,500	7.8	.097	2850
	6.5	.030	9,600			
6 . . .	3.5					
	5.2	.288	11,520	8.4	.300	4800
	4.5					
7 . . .	5.5	.202	8,400	10.5	.185	2160
		.207	8,640	..	.105	2400
8 . . .	4.6	.181	12,960	13.4	.323	3480
9 . . .	5.0	.749	12,480	7.0	.317	5280
		.352	8,160	6.5	.196	4950
	9.2	.134	6,720			
10 . . .	3.4	.235	8,400			
11797	9,360	9.8	.182	2120
	5.7	.598	11,520	9.9		
12	4.8	.147	1750
				13.2	.466	1150

TABLE 2.—TOTAL IODINE IN BLOOD AND URINE IN 12 PATIENTS WITH DIABETES INSIPIDUS.

	Blood iodine, meg. per 100 cc.	24-hour urine, iodine, mg.	24-hour urine, volume, cc.
<i>No Pituitrin.</i>			
Average	5.8	.319	9460
Range	3.0-12.6	.028-.936	
<i>On Pituitrin.</i>			
Average	9.4	.189	2860
Range	4.2-17.8	.078-.466	

An analysis of these findings suggests that in an untreated case of diabetes insipidus, there was an increased excretion of iodine in the urine and an associated low normal level of iodine in the blood. In contrast, when these patients were treated with pituitrin the opposite occurred. The excretion of iodine in the urine was diminished and the blood iodine level was increased.

In a case with diabetes insipidus and pineal tumor given pituitrin and Roentgen-ray therapy, the blood iodine level was low and there

was some increase in the iodine excretion in the urine, as shown in Table 3. Roentgen-ray therapy may have been a factor in the results of this case.

TABLE 3.—IODINE IN THE BLOOD AND URINE OF A PATIENT WITH DIABETES INSIPIDUS AND PINEAL TUMOR.

Case No.	On <i>pituir</i> in.		
	Blood iodine, mcg. per 100 cc.	24-hour urine, iodine, mg.	24-hour urine, volume, cc.
15	3.2	.201	2100

In the 2 patients with diabetes insipidus who were relieved of their polyuria and polydipsia following total thyroidectomy, the blood iodine levels were low, ranging from 1.5 to 4.8 micrograms per 100 cc., and the excretion of iodine in the urine was normal. These results were comparable to those obtained in myxedema, as shown in Table 4. In the usual case of myxedema, the average blood iodine level is 3.5 micrograms per 100 cc. with the method employed.

TABLE 4.—TOTAL IODINE IN THE BLOOD AND URINE OF 2 PATIENTS WITH DIABETES INSIPIDUS 4 YEARS AFTER TOTAL THYROIDECTOMY.

Case No.	No <i>pituir</i> in.		
	Blood iodine, mcg. per 100 cc.	24-hour urine, iodine, mg.	24-hour urine, volume, cc.
13	3.4	.152	4000
14	4.8	.150	2500
	1.5	.094	3300
	3.6		
	4.0	.071	2150
	2.4		
	4.0		

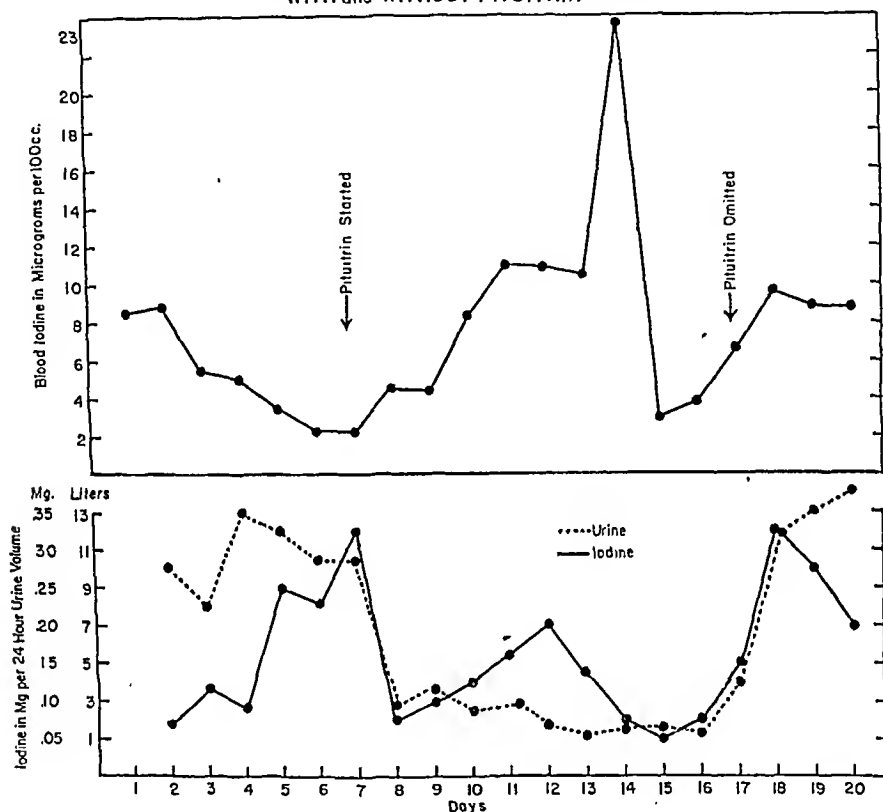
One patient was admitted to the hospital for observation for 20 days. The iodine was determined daily on fasting samples of blood and on 24-hour specimens of urine in order to study the iodine on consecutive days over a period of time. The patient was given a house diet which contained about .150 mg. iodine daily.

The patient took no *pituir*in for 2 weeks before admission to the hospital and her daily urine output approximated 10 liters. The results of her iodine studies are given in Chart 1. During the first 7 days in the hospital, no *pituir*in was administered and her urine volume varied from 8 to 13 liters. During this period the blood iodine level was at first normal and then decreased to a low level while the urine iodine excretion was at first low and then increased considerably. For the next 10 days *pituir*in was injected so that the daily urine volume varied from 2500 to 1200 cc. During this period the iodine excretion in the urine decreased and became low while the blood iodine level increased markedly. These blood iodine results were not fortuitous because the organic and inorganic iodine fractions were determined also and they amounted to the total

blood iodine concentration. However, on the last 3 days of this period, the blood iodine dropped to a very low level. Finally, pituitrin was omitted again for 3 days and the urine volume ranged from 12 to 14 liters; the iodine excretion increased again and the blood iodine remained at a high normal level for 3 days, the final period of observation.

CHART I

IODINE in BLOOD and URINE in a PATIENT WITH DIABETES INSIPIDUS (Mrs. MA)
WITH and WITHOUT PITUITRIN



The iodine content of pituitrin was determined to ascertain whether it contained appreciable amounts of iodine. The iodine concentration was found to be .080 mg. per 100 cc. pituitrin. This amount was considered insufficient to influence blood and urine results.

Blood Iodine Fractions. The fractionation of the iodine of the blood was carried out in 11 cases by methods reported elsewhere.¹¹ This was done in an endeavor to find if the proportion of organic to inorganic iodine in the blood of patients with diabetes insipidus was different from that found in normal individuals and in patients with hyperthyroidism and with myxedema. The approximate proportions of organic to inorganic iodine are 65 to 35 in the normal; 55 to 45 in hyperthyroidism; and 40 to 60 in myxedema with the methods used. In this connection, the results of this study indicated that the relationship of the organic to inorganic blood iodine was not con-

sidered to be abnormal in these cases for their total blood iodine level, whether or not pituitrin was administered (see Table 5). In a few of the cases, the normal relation of the organic and inorganic iodine was reversed. The significance of this is not apparent. Since both the organic and inorganic blood iodine fractions were determined independently of the total blood iodine, it will be noted that the sum of the fractional analyses did not always equal the total. In most instances, however, the results are within the limits of experimental error for methods of blood iodine analyses.

TABLE 5.—TOTAL BLOOD IODINE AND ITS FRACTIONS IN 11 PATIENTS WITH DIABETES INSIPIDUS.*

Case No.	<i>Pituitrin.</i>			<i>No pituitrin.</i>		
	Total blood iodine, mcg. per 100 cc.	Iodine, organic, ethyl alc., mcg. per 100 cc.	Iodine, inorganic, mcg. per 100 cc.	Total blood iodine, mcg. per 100 cc.	Iodine, organic, ethyl alc., mcg. per 100 cc.	Iodine, inorganic, mcg. per 100 cc.
1	4.3	4.0	0.0	3.0	3.1	0.0
2	17.0	14.6	2.2	3.6	3.3	
3	12.0	5.0	7.2	7.0	7.5	
4	6.8	7.1	1.8			
5	6.5	6.4	..	7.8	6.1	2.4
	7.8	5.0	2.2			
6	4.5	4.2	
7	10.5	2.6	7.4	5.5	5.3	1.3
8	5.2	4.5	2.2
9	6.5	3.3	5.5	9.2	4.0	6.1
	4.4	4.2	2.2	8.8	2.5	5.1
	8.4	5.8	3.0	5.2	2.0	2.9
	11.0	6.7	4.3	9.6	4.7	5.0
	23.2	15.6	8.4	8.6	6.5	2.2
13	3.4	0.0	3.5
14	4.0	3.1	2.4

* Cases 13 and 14 had total thyroidectomies performed 4 years previously.

Iodine in Thyroid Glands. From the foregoing observations, there appeared to be an increased excretion of iodine in the urine of patients with diabetes insipidus. Consequently, it seemed of interest to determine whether the iodine content of the thyroid gland in diabetes insipidus was diminished by the increased excretion of iodine in the urine. As the result, the total quantity of iodine was determined in the thyroid glands of 2 patients with this disease who had had these glands removed previously. As control tests, the iodine was determined in the normal thyroid glands of 2 cardiac patients who had total thyroidectomies for the relief of cardiac decompensation. These results are given in Table 6. In the patients with diabetes insipidus, there was .402 mg. of iodine per gm. of wet tissue and the total amount of iodine in the whole thyroid glands was 6.96 mg. and 8.22 mg. In the control thyroid glands, there was .605 mg. and .500 mg. iodine per gm. of wet tissue and the whole of these glands contained 11.1 mg. and 15.0 mg., respectively. These results suggest that there is a decreased amount of iodine in the

thyroid gland of patients with diabetes insipidus. Nevertheless, it must be remembered that this is a small series.

TABLE 6.—IODINE IN THYROID GLANDS OF 2 PATIENTS WITH DIABETES INSIPIDUS COMPARED WITH 2 CONTROL THYROID.

Case No.	Iodine per gm. wet tissue, mg.	Iodine in whole thyroid gland, mg.
<i>Diabetes Insipidus.</i>		
A402	6.96
B402	8.22
<i>Cardiac Controls.</i>		
1605	11.07
2500	15.01

Iodine Tolerance Tests. Iodine tolerance tests were made in 3 cases in order to determine whether the thyroid gland has an extra affinity for iodine similar to the hyperplastic thyroid gland of patients with exophthalmic goiter. The results are given in Table 7. Perkin, Brown and Lang^{12,13} and Fitz and Hunt⁵ have shown by means of these tests that when persons with hyperthyroidism are given a specific amount of iodine, the iodine in the blood does not rise as high as in normal persons and returns to the basal level more rapidly. In contrast, when patients with thyroid deficiency are given iodine intravenously, the blood iodine rises to higher levels than normal and falls more slowly to the basal level and a greater amount of iodine is recovered in the urine.

TABLE 7.—IODINE TOLERANCE TESTS IN 3 PATIENTS WITH DIABETES INSIPIDUS.

Case No.	Hours after iodine test meal.	<i>No pituitrin.</i>	<i>Pituitrin.</i>
		Blood iodine, meg. per 100 cc.	Blood iodine, meg. per 100 cc.
5	0	9	7
	$\frac{1}{2}$	275	84
	1	355	57
	$1\frac{1}{2}$	274	38
	$2\frac{1}{2}$	262	56
6	0	6	
	$\frac{1}{2}$	93	
	1	134	
	$1\frac{1}{2}$	69	
	2	109	
3	0	6	7
	$\frac{1}{2}$	248	230
	1	203	200
	$1\frac{1}{2}$	165	163
	2	158	174
Urine, iodine*		48 mg.	25 mg.
Urine, volume		1950 cc.	5900 cc.

* Total iodine excreted in urine during the 24 hours after ingestion of iodine.

In Case 5 when pituitrin was given (see Table 7), the blood iodine curve was much lower than normal and like that observed in hyperthyroidism. When no pituitrin was given, the blood iodine level was more than twice as high as that found in normal people.

In Case 6, the blood iodine curve was normal without pituitrin. In Case 3, the blood iodine curves with and without pituitrin were much the same but about twice as high as normal. However, with pituitrin 25 mg. of iodine was excreted in the urine during the 24 hours after the ingestion of iodine, compared with 48 mg. of iodine when no pituitrin was being administered.

Discussion. The data in this study reveal that in untreated patients with diabetes insipidus there is an increased excretion of iodine in the urine and usually relatively low normal blood iodine levels. It is suggested that the most likely cause for these changes is a washing-out process resulting from the exchange of huge volumes of fluid in these patients and the failure of reabsorption by the kidney. When pituitrin is administered, the blood and urine iodine results are reversed and the fluid intake and output are markedly decreased because of the effect of pituitrin on renal function which increases reabsorption. This idea may be strengthened by the fact that pituitrin diminishes the excretion of iodine in the urine after the ingestion of Lugol's solution. Furthermore, Perkin^{9a} has found high blood iodine levels in patients with chronic nephritis with marked renal insufficiency and edema which indicates a retention of iodine. Diodrast clearance tests¹⁶ made in some of these patients also suggest that pituitrin diminishes the excretion of iodine. Salter¹⁴ believes that the high iodine turnover in these cases may be a washing-out phenomenon like that seen with urea. On the other hand, the possibility of a thyro-pituitary relationship as a cause of these findings should be considered.

Summary. This paper presents a study of the iodine in the blood and urine of 15 patients with diabetes insipidus. In addition, the amount of iodine was determined in the thyroid glands of 2 of these patients who had had a total thyroidectomy.

When the patients were not treated and there were marked polydipsia and polyuria, the average blood iodine was 5.8 micrograms per 100 cc. (range, 3.0 to 12.6). The average 24-hour excretion of iodine in the urine was .319 mg. (range, .028 to .936 mg.). In contrast, when pituitrin was administered, the average blood iodine was 9.4 micrograms per 100 cc. (range, 4.2 to 17.8 micrograms). The average 24-hour excretion of iodine in the urine was .189 mg. (range, .078 to .466 mg.). The relation of the organic to the inorganic blood iodine was considered to be practically normal in these cases. The iodine content of the two thyroid glands was decreased compared with two control thyroid glands.

In untreated patients with diabetes insipidus, there appears to be an increased excretion of iodine in the urine and usually relatively low normal blood iodine levels. When pituitrin is administered, the excretion of iodine in the urine diminishes and the blood iodine level increases. These findings may represent a failure of reabsorption of iodine by the kidney which is altered by pituitrin administration.

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STUDIES OF THE EXPECTORANT ACTION OF IODIDES.*

By LOUIS TUFT, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, TEMPLE UNIVERSITY SCHOOL OF MEDICINE; CHIEF, CLINIC OF ALLERGY AND APPLIED IMMUNOLOGY, TEMPLE UNIVERSITY HOSPITAL

AND

NATHANIEL M. LEVIN, M.D.,

FORMERLY FELLOW IN BRONCHOSCOPY, TEMPLE UNIVERSITY HOSPITAL
PHILADELPHIA, PA.

(From the Clinic of Allergy and Applied Immunology and the Jackson Bronchoscopic Clinic, Temple University Hospital and School of Medicine.)

THE clinical use of the expectorant group of drugs is widespread but their use is predicated purely upon an empirical basis. The little that is actually known of the mode of action of these agents has been derived from clinical experience in the treatment of respiratory diseases, both infectious and allergic in character. Our interest in expectorants arose some time ago in attempting to find a drug which would be most effective in liquefying the extremely viscid secretions of the asthmatic patient, especially of the chronic type or of those in status asthmaticus.

Search of the literature revealed a definite lack of data concerning the mechanism by which expectorants produce their effects. The earliest attempts to prove that expectorant drugs actually were effective were carried out with ammonium compounds and were performed at first in animals. However, Coleman¹ in 1916 observed the effects of ammonium compounds in 7 human cases of bronchitis and showed by rather crude methods that the drug was excreted in the sputum as indicated by an increase in the ammonia N.

* Read before the meeting of the Association for the Study of Allergy, New York, June, 1940.

More recent work with expectorants, especially that carried out in animals by Gordonoff and his coworkers abroad, has made it possible to classify these drugs on a more logical basis. From these experiments, Gordonoff² concluded that the action of expectorants depends upon the predominance of one of two factors: 1, stimulation of the smooth musculature of the bronchi, termed the *excretomotor* action of the drug, which is either a manifestation of increased bronchial peristalsis or a wavelike motion dependent entirely upon the movement during the respiratory act; and 2, liquefaction of the bronchial secretions by actual excretion of the drug into the bronchi and subsequent delay in resorption of these secretions, which is called *secretolysis*. Drugs belonging to the excretomotor group include ammonium chloride, guaiacol, thymol and ether. In the secretolytic group are: iodides, saponin, sugars and sulphur. Gordonoff concluded that efficient respiration is essential for the action of any expectorant and that the expectorant to be used in a specific case should be chosen according to the type of secretion already present; that is, it should be secretolytic if the secretion is scanty and excretomotor if it is fluid and abundant. He feels that sedatives do more harm than good, as they depress respiration and cancel the effect of good respiratory movement upon the expectorant action of the drug.

It was evident, therefore, from a review of the literature that nearly all the evidence as to the action of expectorants was based upon the results of animal experiments. It occurred to us that it might be possible to study the expectorant action of various drugs in the human with the aid of the bronchoscope. Our plan was to administer the drug to be studied either parenterally or orally and then to aspirate the bronchial secretions by the bronchoscope. The condition of the bronchial mucosa was to be observed during the process, if at all feasible. The secretions thus obtained then were to be studied chemically for the presence of ions not usually or normally detectable. This was the general plan adopted although certain departures from it were necessary, as when the drug was given orally. It was decided to start with the iodides since a simple test was available for the detection of the iodide ion.

Review of the literature as to the effect of iodides indicated that the iodides render colloids more soluble and less viscid *in vitro*, although Sollman⁵ doubts whether this actually is the case in the concentration reached therapeutically. There is evidence of iodides being excreted into the saliva and urine but not into the bronchial secretions in humans, although Stieglitz⁶ by postmortem staining methods showed the presence of the iodide ion in the bronchial mucosal cells as well as in other parenchymatous secreting cells. As previously noted, iodides are believed to belong to the secretolytic group. Thus Gordonoff and Merz⁴ showed that iodides will decrease the density of a contrast medium introduced into the bronchi of rabbits. Gordonoff and Lehmann³ also were able to show

a delay in absorption of a sugar solution introduced into the bronchi of rabbits. From these experiments the conclusion was reached that the action of iodides is mainly due to excretion into the bronchial tree, with subsequent delay in resorption of the secretions already present. The latter actions thus make the respiratory act and the coughing mechanism more effective in raising these secretions. The motor stimulation noticeable with ammonium chloride was almost entirely lacking in iodide administration. These conclusions were arrived at by inference from the experimental data, since the actual presence of iodides was not demonstrated nor was any information obtained as to how soon the iodides appear in the bronchial secretions or how long it remains; also whether there was any difference noted when the drug was given by mouth as contrasted with intravenous injection. It was known, however, that iodides were readily absorbed from the gastro-intestinal tract, being given usually in the form of potassium iodide in doses of 4 to 8 gm. The usual intravenous dose was 1 to 2 gm., although up to 10 gm. could be safely given. It was decided to carry out the initial experiments with the iodide being given intravenously and to compare it subsequently with the oral route.

Procedure. Our first experiments were carried out in dogs but without success, since satisfactory data could not be obtained. We, therefore, discarded attempts at further animal experimentation and proceeded at once to experiment in the human. The patients utilized were patients from the allergy or bronchoscopic departments who had either asthma, bronchiectasis or other pulmonary conditions requiring bronchoscopic examination or treatment. The general procedure followed in each case consisted first in the insertion of the bronchoscope and the aspiration of a control specimen of secretion into the special glass containers utilized for that purpose. Sodium iodide was then injected intravenously in doses of 15 to 31 grains. Following the injection, specimens of the secretions were withdrawn in like manner at 5-minute intervals for the duration of the time it was feasible to retain the bronchoscope. The specimens thus obtained were then tested in the laboratory for the presence of iodides. The method used was a purely qualitative one but was sufficiently sensitive to detect very minute amounts of iodides as determined by preliminary control tests. The procedure was briefly as follows: Organic matter was destroyed by heating the material to be treated with a strong solution of potassium hydroxide in a tube or crucible. It was then extracted with water and the extract tested for the presence of iodine by the addition of a starch solution. A definite blue color was taken as positive (+), faint blue as doubtful (\pm) and absence of color as negative (-).

In order to obtain information as to the excretion of the iodides through other channels, in 4 patients specimens of saliva were aspirated into a separate container at the same time that the bronchoscopic specimens were collected. These were likewise examined

for iodides in the same manner as the bronchial secretion and the appearance time noted. Urine specimens also were collected by 4 patients, both before and at intervals after the iodide injection and examined by direct test for iodides.

Having determined the approximate appearance time of the iodides in the bronchial secretion after intravenous injection and its probable persistence, we next attempted to determine the appearance time after oral ingestion. Accordingly, a group of 9 bronchoscopic patients were given 60 grains of potassium iodide contained in 1 dram of an aqueous solution orally immediately prior to bronchoscopic examination. The time at which the first specimen was aspirated was noted and one or in some instances two specimens of secretion were aspirated in similar manner as in the intravenous group. These were then examined for iodides. Aspiration of repeated specimens at 5-minute intervals was not deemed necessary in this group, as we were interested only in the appearance time in comparison with that of intravenous group.

Results. The results of the experiments in the group given the iodides intravenously are shown in the following chart:

CHART 1.—EXCRETION OF IODIDE AFTER ITS INTRAVENOUS INJECTION.

Bronchial Secretion.

Case and amount.	Control.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.	Urine.		Saliva pos. at.
									Neg.	Pos.	
Mr. W. 30 gr.	0	0	±	+	+	+					
Mr. F. 15 gr.	0	±	±	+	+	+					
Mr. F. 30 gr.	0	0	±	+	+	+	+	±	45"	1' 30"	
Mr. L. 30 gr.	0	0	+	+	+	+			50"	1' 30" 2' 0" 5' 0"	10-30 mm.
Mr. J. 15 gr.	0	0	0	+	+	+	0	0	1' 15"	1' 55" 4' 40"	20-40 mm.
Mr. L. 31 gr.	0			0	+	+	+	+			20-40 min.
Mr. S. 31 gr.	0	0	+	+	+	0			1' 0"	1' 30" 3' 0"	10-30 min.

It will be noted that while a trace of the iodide was detectable in 1 patient after 10 minutes, it was a little more pronounced at 15 minutes, definite at 20 minutes in all but 1 instance and definite in all cases at 25 minutes. In the 2 cases receiving only 15 gr., little difference was noted from those receiving twice as much; in fact, in Mr. F., who received 15 gr. on one occasion and 30 gr. on another, little difference was observed. This might be taken to indicate that the quantity injected has little or no effect upon the appearance time.

The bronchoscope could not be retained long enough in every patient to determine the time at which the iodides disappeared from the bronchial secretion. In one instance (Mr. S.) it was no longer evident at 30 minutes, in another (Mr. J.) at 35 minutes and in a third (Mr. F.), only a trace was present at 40 minutes. It is interesting to note that no evidence of the iodide was present in the urine of these 3 patients examined at 60-minute, 75-minute and 45-minute intervals respectively, but did appear subsequently. In a fourth patient (Mr. L.) the urine was negative at 50 minutes but was positive at 90 minutes. This might be taken to indicate that the iodide present in the bronchial secretion first is resorbed into the blood and then is excreted into the urine by the kidney, rather than being immediately excreted by the kidney.

In the 4 patients in whom salivary studies were carried out, the iodides first appeared in 10 minutes in 2, and in 20 minutes in the other 2. This corresponded roughly to the time of appearance in the bronchial secretions, with possibly a little earlier appearance for the salivary group.

It was difficult under the conditions of the experiments to determine whether the amount of bronchial secretion was increased by the iodides or to detect any changes in the bronchial mucosa as compared to that preceding the iodide injection. While attempts were made to determine these facts, no significant conclusions could be drawn.

CHART 2.—EXCRETION OF IODIDE AFTER ITS ORAL INGESTION.

Case.	5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.
Mr. F.	0							
Mr. S.	0							
Mr. O.			+					
Mr. A.			0	±				
Mr. G.				+				
Mr. T.						+		
Mr. S.						0		
Miss D.						+	+	
Mr. R.								0

All patients received 15j sat. solution of pot. iodide.

The results of the experiments in the group who received the iodides orally are shown in Chart 2. As in the intravenous group, the iodides appeared in the bronchial secretions of 3 patients in 15 to 20 minutes and at longer intervals in the others. While this

may be taken to indicate a somewhat slower excretion after oral administration, this conclusion cannot be made definitely because of the conditions of the experiment. Nevertheless, the primary purpose of the experiment, namely, that iodides appear in the bronchial secretion after oral administration was fulfilled by these experiments.

Comment. The results obtained indicate that iodides are excreted into the bronchial tree from the blood. The time taken before this excretion occurs is somewhat variable, but it takes place within 15 to 25 minutes after intravenous injection. The excretion probably is a little slower when given orally than when given intravenously, but this difference could not be definitely determined and is not significant in clinical application. The intravenous administration offers no important advantage over the oral method, especially in view of the added work entailed in its use. The salivary excretion of iodides occurs promptly, although it is hard to determine under the conditions of the experiment, but urinary excretion is delayed. This may be taken to indicate that the salivary glands and bronchi act as the selective excretory organs for this drug and that urinary excretion must await resorption from the bronchi and gastro-intestinal tract. This is similar therefore to Gordonoff's findings in the experimental animal.

Conclusion. We have been able to demonstrate for the first time at least in the human that iodides given either orally or intravenously are excreted into the bronchial secretion within 15 to 25 minutes. We believe that this excretion probably accounts for the action of iodides as expectorants and that oral administration probably is just as effective as intravenous and less troublesome.

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THE DIAGNOSTIC VALUE OF THE TAKATA-ARA REACTION.

By THEO R. WAUGH, M.D., C.M.,

PATHOLOGIST-IN-CHIEF OF ROYAL VICTORIA HOSPITAL; ASSOCIATE PROFESSOR OF
PATHOLOGY, MC GILL UNIVERSITY,

AND

RICHARD D. MCKENNA, M.D., C.M.,

HOUSE PATHOLOGIST, ASSISTANT DEMONSTRATOR IN PATHOLOGY,
MONTREAL, CANADA.

(From the Departments of Pathology of the Royal Victoria Hospital and McGill University.)

SINCE the introduction of the Takata-Ara reaction in 1925 a considerable amount of literature has accumulated on the subject. This has been thoroughly reviewed by Magath,² Wayburn and

Cherry,⁵ and others. Two facts stand out conspicuously from such reviews: first, that we are still ignorant of the mechanism of the reaction; and, second, that a marked difference of opinion exists as to its diagnostic value. This difference would appear to be due to lack both of uniformity in the technique employed and of precision in reading the results of the reaction. In an effort to contribute something toward settling the question of the value of the test, we have recently reviewed a series of cases on which the reaction was performed and the results of our investigation are given below.

No detailed historical sketch of the Takata-Ara reaction will be attempted. Suffice it to mention that the test was described in 1925 by Takata^{3,4} and Ara⁴ for the study of four widely separate diseases, namely, syphilis, meningitis, pneumonia and tuberculosis, and that Jezlar⁷ in 1929 modified the technique and used the test as a diagnostic measure for cirrhosis of the liver. Since this time many American, English, German, French and Italian workers have reported their findings on a variety of different lesions, using various modifications of a basically similar technique. Most of the interest in the test has throughout been in its merits as a diagnostic measure in hepatic cirrhosis.

The mechanism of the Takata-Ara reaction, much discussed, remains obscure. It is even uncertain whether flocculation occurs because of the absence from positively reacting plasmas of some protein normally exerting a "protective colloid" effect or because of the presence in such plasmas of a protein or other substance exceptionally apt to form precipitating complexes with the mercuric reagent. In this regard it is of interest that no flocculation occurs when saline is substituted for plasma in performing this test. In any case our own observations lead us to believe that positive reactions are not due either to mere abnormalities of the A/G ratio because of lowered albumin content or to the presence of increased fibrinogen, as Wuhrmann and Leuthardt⁶ have suggested. On the other hand, as regards absolute increase in the plasma globulins, in this institution where plasma protein determinations are done by the salting-out method, figures are available on 10 of the 23 positive or plus-minus reactors analyzed below. In all but 1 an actual increase in the plasma globulins was found. The question of the separation of these globulins has undergone a metamorphosis in the past few years and is still in some debate. However, it is of interest that more recent techniques¹ indicate an increase in the beta-globulin fraction in cases of cirrhosis of the liver.

Technique. A great deal of the discrepancy that has arisen in the evaluation of the Takata-Ara test is apparently due to differences in the methods employed in carrying out the reaction and in reading and interpreting the results. For this reason, a detailed description of the method that we have been using for some time is included in this article.

The test may be done on blood serum, plasma, or transudates, such as ascitic fluid. Most of our results were obtained from oxalated plasma

procured at the time of carrying out a complete hemogram. Blood is usually taken for such tests in the morning, between 10 and 12 o'clock to avoid any effect of digestive processes on the plasma. At least, 1 cc. free from hemolysis and cells, is required.

A series of 8 tubes, approximately 10 cm. in length and inner bore of 1 cm., are placed in a rack. The tubes must, of course, be thoroughly clean. One cubic centimeter of 0.9% NaCl is pipetted into each tube and 1 cc. of plasma added to the first tube. This is mixed with the saline by shaking and 1 cc. of the mixture withdrawn and placed in the second tube. By continuing in this manner and discarding 1 cc. from the last tube a series of increasing dilutions ($\frac{1}{2}$ to $\frac{1}{256}$) of plasma in saline is set up. To each tube first 0.25 cc. of a 10% solution of sodium carbonate and then 0.15 cc. of 0.5% bichloride of mercury are added. Complete mixing is obtained by shaking after each solution has been placed in the tube. A slight precipitate, which disappears on shaking, may occur after addition of the mercury. The series of tubes is then allowed to stand at room temperature for 24 hours.

At the end of this interval, the result of the test is read by estimating the amount of precipitate in each tube. This is expressed as 0, T (Trace), 1, 2, 3 or 4. Precipitates classed as "4" occupy approximately the lower third of the solution in the tube. In doubtful cases, accurate reading of the amount of precipitate may be accomplished by thoroughly shaking up the tube and filling a Wintrobe sedimentation tube to the 10-cm. mark with a portion of the contents. The Wintrobe tube is then centrifugalized at high speed for 15 minutes. Less than 1 mm. of whitish sediment in the bottom of the tube is classed as a trace (T), 1 to 2 mm. as "1," 2 to 3 mm. as "2," and so on. Any amount over 4 mm. is designated "4."

The Takata-Ara reaction is positive when two adjacent tubes show a Grade "4" degree of precipitate and the next tube is at least a Grade "3," for example (00T24441) or (00134421). Plus-minus reactions are reported whenever the criteria for the positive reaction are not reached, but at least two tubes show a Grade "3" sediment, for example (00T12431), (0001331) or (000TT332). All reactions of lower degree are negative as (000TT231) or (000TT1TT). It would appear from an analysis of our findings that accurate reading of the reaction is extremely important.

Analysis of Results. The present study covers an analysis of 300 consecutive tests carried out in our laboratory using the technique described above. Most of them were done on oxalated plasma obtained at the time of doing a complete morphologic blood study on cases where a hyperbilirubinemia was present or in which there was some reason to at least suspect the presence of hepatic disease. Using the criteria of reading the reaction given above, 277 cases are to be classified as negative, 11 as plus-minus, and 12 as positive. Each of these groups will be analyzed separately.

Almost all of the negative Takata-Ara reactions were carried out on different patients. There were a few individuals, however, in which the test was repeated at a later date. It will be recalled that the reaction is designated as negative whenever no two adjacent tubes show at least a "3" degree of precipitate. In the vast majority of these reactions only a trace of sediment was present.

Study of the case records of the patients on whom the 277 negative reactions were obtained reveals that in 11 a clinical diagnosis of cirrhosis was made. Only 2 of these, however, were positively

confirmed by histologic examination of the liver. In 1 of these a biopsy showed a very early periportal cirrhosis, while the other case was autopsied and a typical atrophic cirrhosis was found. However, on 2 other occasions this patient gave strongly positive reactions. In this connection it is interesting to note that in another case which was undoubtedly cirrhosis but was not autopsied, both positive and negative reactions were obtained at different times. A reasonable doubt may be cast on the clinical diagnosis of cirrhosis in 5 of the remaining cases. This leaves 4 of the 11 with negative reactions in which the diagnosis seems quite certain and positive results were never obtained.

It is apparent, therefore, from the findings in this group that cases of cirrhosis do occur with negative Takata-Ara tests. In some of these the negative reaction is transient, and this interval may be preceded and followed by periods during which it is positive.

Plus-minus reactions were obtained in 11 cases. Three of these were clinically quite typical Laennec's cirrhosis and 1 of the 3 was proven later by autopsy. Four of the 11 occurred in individuals having cholangitis with a variable amount of biliary cirrhosis; 1 of these was due to malignancy and 2 to cholelithiasis. Of the 4 remaining cases, 1 was an arsenical hepatitis and another a lymphosarcomatosis with extensive spread in the liver. This leaves only 2 of the 11 cases in which there was no particular involvement of the liver. One was an advanced pulmonary tuberculosis with marked destruction of the adrenals and the other a multiple myeloma.

From these findings it would appear that plus-minus reactions may be considered strongly suggestive of some form of hepatic disease and more particularly a peri-insular or biliary form of cirrhosis.

Reactions were designated positive in 12 cases. Of these, 9 were proven subsequently to be peri-insular cirrhosis by postmortem examination and 2 more were quite typical of this disease clinically. The remaining case of the 12 had a marked obstructive jaundice which was believed due to malignancy. He left the hospital without operation so this diagnosis has never been confirmed pathologically.

From this group one may conclude that Takata-Ara reactions with sufficient precipitate to be classified as positive according to the criteria outlined above occur almost exclusively in cases of peri-insular cirrhosis.

Conclusions. Analysis of a series of 300 Takata-Ara reactions, carried out for the most part on patients who showed a hyperbilirubinemia or gave reason to suspect the presence of hepatic disease, indicates that the test has considerable diagnostic value. It would appear that the difference of opinion which has arisen in the literature concerning its value is due to the use of various techniques and a lack of precision in reading the results. A means is described whereby more accurate results may be obtained.

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ACTIVATED STEROLS AND CALCIUM SALTS IN TREATMENT OF PARATHYROID TETANY.

BY ELMER L. SEVRINGHAUS, M.D.,

PROFESSOR OF MEDICINE, UNIVERSITY OF WISCONSIN; PHYSICIAN TO WISCONSIN
GENERAL HOSPITAL, MADISON, WIS.

(From the Department of Medicine, University of Wisconsin.)

McLEAN has pointed out² that there is much evidence to suggest the essentially equivalent therapeutic values of dihydrotachysterol and vitamin D preparations for oral treatment of hypoparathyroidism. This conclusion is based on the lack of any decisive evidence to the contrary, on clinical reports which indicate satisfactory comparisons, and on toxicity experiments with small laboratory animals. The data from this latter type of trials are presented as follows: The "borderline toxic doses" of pure calciferol (crystalline vitamin D₂) are from 5 to 12.5 times as great as for crystalline dihydrotachysterol. Using the figure 5 as representing maximum toxicity, which McLean believes is parallel to potency in maintaining serum calcium level, pure calciferol would be not over one-fifth as potent as the dihydrotachysterol. By definition, 1 mg. of calciferol, or vitamin D₂ is equivalent to 40,000 international or U.S.P. units. The commercial form of dihydrotachysterol, now marketed as "Hytakerol," is a 0.2% solution of pure activated sterol, or 0.5% of the basic sterols, only 40% of which are significantly active. With the above equivalents in mind 1 mg. of calciferol, or 40,000 international units, of vitamin should be as active as 0.2 mg. of dihydrotachysterol, which is contained in 0.1 ml. of the commercial oily solution. Or, in other words, 1 ml. of the oil solution, containing 2 mg. pure dihydrotachysterol (or 5 mg. basic sterols) would be equivalent to 400,000 international units of vitamin. McLean points out that the use of a small unit for the vitamin standardization has tended to discourage the use of large enough doses to demonstrate this usefulness in treating tetany. Doses of Hytakerol commonly in use vary from 0.25 to 2 ml. daily, corresponding to 100,000 to 800,000 units of vitamin D.

An opportunity to test this suggestion was based upon the treatment of 4 cases of tetany which had been under observation for some time previous to the trials to be described. In each of these

patients the beneficial results of appropriate doses of the vitamin as well as of the special preparation have been demonstrated. The choice of therapeutic agent is therefore made a matter of cost and availability of medicament.

CASE 1.—V. T. R. (No. 209579) was first seen at age 27 because of marked thyrotoxicosis, for which a two-stage thyroidectomy was performed, with excellent general results. Although no clinical notes of tetany were found in the convalescent record, and the serum calcium was known to be 9 mg. per 100 cc. on the fifth postoperative day, the patient later mentioned that paresthesias appeared at about the time of discharge from the hospital. She was readmitted 4 months later with the typical symptoms of tetany, including laryngeal stridor and carpal spasm which required use of intravenous calcium gluconate for relief. The following morning serum calcium was 8, phosphorus 6, whole blood cholesterol 129 mg. per 100 cc. The basal metabolic rate was +4%.

Treatment was based on use of a low phosphorus diet, which was continued throughout the observations. Calcium chloride was given in 25% solution, 8 gm. daily. With Hytakerol, given in doses of 0.5 ml. daily, serum calcium was maintained at 10.1 to 10.6 mg., phosphorus dropping to 3.7 and later 2.7 mg. during the first 3 months. The dose of sterol was reduced to 0.25 ml. daily with equally good control, but 0.125 or 0.2 ml. per day led to a drop in calcium to 8.8 mg. and return of tetanic symptoms in mild form.

Transfer was undertaken to vitamin D, using "Ertron," a Whittier process concentrate with 50,000 units per capsule. Dosage of 100,000 units daily for 2 months was not entirely adequate, but 125,000 units was successful, and serum calcium was 9.9 mg., phosphorus 3.7 mg. after 1 week at the higher dose, which eliminated all symptoms of tetany. Return to use of Hytakerol, 0.5 ml. alternate days (0.25 ml. daily), was symptomatically as good, with calcium 9.7 mg., phosphorus 2.5 mg.

These results indicate that 0.25 ml. Hytakerol and 125,000 international units of Ertron are nearly equally potent. It is of importance to the patient, at least, that the former costs just 33% as much as the latter preparation.

CASE 2.—H. P. (No. 221007) was first seen at age 58, some months after thyroidectomy had been done elsewhere, and at which time she showed congestive heart failure and tetany. Serum calcium was 4.5 mg., phosphorus, 2.5 mg. per 100 ml. Treatment with low phosphorus diet and calcium chloride, 4 gm. daily, was insufficient and she was given "Drisdol," a propylene glycol solution of vitamin D. Dosage was uncertain and irregular as an ambulatory patient, and she was hospitalized a second time after a month's interval. With Drisdol doses of 100,000 units daily for 2 weeks, calcium rose from 7.9 to 10.1 mg., phosphorus rising from 2.9 to 3.2 mg. Then the dose was reduced to 50,000 units daily, with calcium dropping to 8.6 mg. and rising to 9, 9.9 and 10.2 mg. in the course of 3 weeks. She was then transferred to use of Hytakerol, 0.25 ml. daily, and after 2 weeks calcium had dropped from 10.2 to 9.2 mg. but phosphorus remained at 3.1 mg. Tetanic symptoms remained in abeyance throughout the period of treatment with vitamin or dihydrotachysterol.

These results suggest that 0.25 ml. Hytakerol is not quite as adequate a dose as 50,000 units of Drisdol. This is a more favorable comparison for the vitamin than the first case, but it is again

significant that the vitamin cost to the patient would have been exactly 3.5 times as great, although both preparations are produced by the same firm.

CASE 3.—D. E. (No. 96338) was first seen at age 21 because of lesions of the nails, skin on hands and feet, and on the tongue associated with allergic sensitivity to monilia. Other findings included numerous minute cataracts in both lenses, positive Chvostek and Trousseau signs, Roentgen ray evidence of markedly increased density of all bones, calcification in brain substance, and serum calcium 8, phosphorus 6.4 mg. per 100 ml. The history indicated that idiopathic tetany had been recognizable since age 5. The treatment of tetany began with the diagnosis at age 21, and was based on low phosphorus diet, a daily intake of added calcium salts, and minimal doses of dihydrotachysterol to abolish all symptoms of tetany. Following each of the trials of lower dosage it has been found necessary to return to 1 ml. daily of Hytakerol. A dose of 0.75 ml. has allowed the recurrence of tetany, whereas doses of 1.5 to 2 ml. cause the serum calcium to rise to 11 to 11.8 mg. Use of the 1 ml. doses daily maintains the calcium at 8 to 9.3 mg., phosphorus 3.3 to 6.1 mg., usually in the lower range, and with entire freedom from tetanic symptoms or signs. After 3 years of such treatment an attempt was made to substitute vitamin D preparations for the dihydrotachysterol. The patient had been economizing by use of 0.75 ml. of the latter preparation for some time, was usually free from symptoms, and had calcium 9.2, phosphorus 5.3 mg. per 100 ml. at the time of change. She was given Mead's viosterol in oil, 10,000 international units per gm., the daily dose being 100,000 units. This was continued for 3 weeks, during which calcium varied from 8.7 to 9.35 mg., and phosphorus was 4.8 mg. No tetanic symptoms occurred. The return to Hytakerol, 1 ml. daily, maintained the calcium at 8.3 to 9.3 mg. but induced a progressive drop in phosphorus to 3.3 mg.

Such findings suggest the essential equivalence of 100,000 international units of viosterol with 0.75 ml. of Hytakerol. At current retail prices the vitamin preparation costs twice as much as the Hytakerol, which led the patient to return to the latter for maintenance.

CASE 4.—C. I. (No. 10759) was first seen at age 53, when she developed acute tetany after thyroidectomy for thyrotoxicosis. Subsequent studies have proved that the tetany is of permanent type. Over a period of 5 years she has had treatment of variable effectiveness, with dietary co-operation far from uniform. During the first year small doses of viosterol, not over 30,000 units, were employed, and supplemented with parathyroid extract. Dihydrotachysterol was first used after more than 2 years with tetanic symptoms. Persistent tendency to frequent, loose stools made control of tetany doubly difficult and seldom responded to any treatment other than use of teaspoonful doses of camphorated tincture of opium after each bowel evacuation. Almost 5 years after the onset of tetany a comparison was made between two vitamin D preparations and dihydrotachysterol. Keeping the patient on low phosphorus and low residue diet, with 3 gm. of calcium chloride added daily $\frac{1}{2}$ hour before meals, she was given 100,000 international units of "Drisdol," the solution of D in propylene glycol. After 10 days the dose was increased to 200,000 units daily. One week later still the vitamin was supplied by "Deltalin," a Lilly capsule containing 50,000 international units each, administering 200,000 units daily. During this entire period of $3\frac{1}{2}$ weeks serum calcium had changed

from 5.8 to 7.6 mg., phosphorus from 5.5 to 5.8 mg., and tetanic symptoms and signs were usually in evidence. Treatment was then shifted to Hytakerol, with doses of 0.5 ml. for 1 week, 0.75 ml. for 10 days, and, finally, 1 ml. daily. With the use of the larger dose serum calcium rose to 8.8 and 9 mg., phosphorus decreased to 4.4 to 5.5 mg. and tetany was completely relieved.

The results obtained with this patient do not give exact equivalent doses, but indicate that 200,000 units of the vitamin D preparations were perhaps as potent as 0.75 ml. of Hytakerol, certainly not as helpful as 1 ml. Comparing the costs at retail, the dihydrotachysterol would cost one-sixth less than the Deltalin, which had only a brief trial, but Drisdol would cost 4.6 times as much as the Hytakerol, produced by the same laboratory.

Results. The results obtained in studies on these 4 patients are tabulated in Table 1. The result quoted from McLean² is based on his calculation of the maximum potency to be expected from calciferol. The results herein reported suggest that McLean was conservative in his conclusions, and that commercial vitamin D preparations may be more potent than he stated. The limiting factor in turning to the vitamin preparations is neither ineffectiveness nor "toxicity" of any dangerous sort, but a matter of greater cost than the single product containing dihydrotachysterol, Hytakerol.

TABLE 1.—COMPARISON OF ANTITETANIC POTENCIES OF DIHYDROTACHYSTEROL AND VITAMIN D.

Source of comparison.	Dihydrotachysterol, ml. of 0.2% sol.	Vitamin D		
		Preparation.	Dose, I. U.	Equivalent for 1 ml. Hytakerol.
F. C. McLean ²	1.00	Calciferol	..	400,000
Patient V. T. R.	0.25	Ertron	125,000	500,000
Patient H. P.	0.25	Drisdol	50,000	200,000
Patient D. E.	0.75	Viosterol	100,000	133,000
Patient C. I.	0.75	Drisdol	200,000	266,000

The relatively high cost of commercial preparations of viosterol in the United States is due in large part to the fact that no preparations containing more than 10,000 international units per gm. have been permitted in commerce with the approval of the Council on Pharmacy and Chemistry of the American Medical Association or under licenses granted by the Wisconsin Alumni Research Foundation. Preliminary steps are known to be under way which will make available the higher concentrations of viosterol for prescription use only and which, it is hoped, will receive the approval of the agencies such as those mentioned. These procedures will drastically reduce the retail prices of the high potency viosterol materials so that the price comparisons mentioned must be understood as of 1941 retail costs.

Another detail in the management of the patient with chronic tetany is the choice of calcium salt for use in addition to the small calcium content of the low phosphorus diets. Calcium lactate has

been used most widely. Calcium gluconate was advocated because of its solubility, ease of absorption, and slightly sweet taste. Calcium phosphate is often prescribed, although the rationale of adding phosphate is incorrect, and in spite of the known fact that phosphates in the intestinal tract will reduce the absorption of calcium when the reaction is not acid. The optimum calcium salt is calcium chloride, because this salt is very soluble in water, tends to produce a slightly acid reaction favoring absorption, and because it furnishes the largest proportion of calcium per gm. of salt. From the molecular weights it can be seen that 1 gm. of the salts will produce the following amounts of the element calcium: gluconate, 93 mg.; lactate, 185 mg.; chloride, 360 mg. In other words, the chloride is 4 times as effective as the gluconate, twice as effective as the lactate when serving as a source of calcium. The chief drawback to its use in oral preparations has been its highly astringent effect in the mouth and pharynx. This can be masked satisfactorily by prescribing the chloride as a 25% solution in a vehicle such as the standard elixir or syrup of glycyrrhiza. Patients have been kept on this very inexpensive preparation with complete satisfaction, using doses of 2 to 4 drams daily well before meals.

Criticism of the chloride has been made on the ground that use of this salt will add an anion to the urine, and this will tend to increase the loss of cations, possibly thereby increasing calcium loss. To test this possibility trials were made with patient D. E. described above. The data are given in Table 2. The intake of calcium in food and drinking water was essentially constant, providing 0.124

TABLE 2.—EFFECT OF ANIONS ON CALCIUM SALT THERAPY.

3-day period.	Salt used.	Daily dose, gm.	Calcium content, mg.	Urine excretion for 3 days.	
				Volume, ml.	Calcium, mg.
3/25-27 . . .	Gluconate	4 0	372	2580	234
3/28-30 . . .	Gluconate	4 0	372	1560	223
3/31-4/2 . . .	Chloride	4.0	1440	1830	137
4/3-5	Lactate	2.0	370	2290	203

to 0.133 gm. of calcium daily. The use of dihydrotachysterol was discontinued the day before beginning the test, and the patient remained free from tetanic symptoms throughout the 12 days of the study. Serum calcium decreased from 9.2 to 8.7 mg. in this interval. It should be observed that although the chloride provided 4 times as much calcium as the lactate or the gluconate used, and although the extra chlorine to be excreted should increase calcium loss, nevertheless, the urinary calcium was distinctly lower during the period of 3 days' use of chloride than before or after. In spite of the lack of data from fecal analysis to complete information about a calcium balance it is well known that calcium chloride is well absorbed. The maintenance of several patients with this salt for long periods accords with this fact.

The disadvantage of excessive amounts of inorganic phosphate in the intestine when calcium absorption is being facilitated has been stressed by Ellsworth.¹ Attempts have been made to use a proprietary preparation of calcium phosphate, with effervescent salts, in 2 of the patients described in this report, but with failure to control tetany readily in spite of extremely large doses, and with some tendency to increase in serum phosphate. Experience with another patient who has post-thyroidectomy permanent tetany and who requires 0.25 to 0.4 ml. of Hytakerol daily with 4 gm. of calcium chloride, indicates that milk is to be excluded from the diet. When using milk daily the serum phosphate averaged 5.15 mg. for 6 months but when the milk was omitted the phosphate dropped to 4 to 5.1, average 4.7 mg. for 10 months. During these two periods, calcium remained at the same average level of 8.9 and 8.8 mg. but varied from 6.8 to 10.4 mg. while using milk, only from 7.7 to 9.9 mg. when milk was excluded.

Summary. Comparisons in 4 patients with tetany indicate that large doses of vitamin D may serve to control serum calcium and phosphorus levels adequately, but that at current prices this entails an increase in cost to the patient of 2 to 6 times that required for similar success with use of dihydrotachysterol.

Use of calcium as the chloride is advocated, and its superior efficiency in furnishing calcium is combined with safety and palatability when the salt is dispensed as a 25% solution in the syrup or elixir of glycyrrhiza.

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USE OF SULFATHIAZOLE IN INFECTIOUS MONONUCLEOSIS.

By H. T. HOFFMAN, M.D.,

STUDENT HEALTH SERVICE,

H. D. LEES, M.D.,

ASSOCIATE PROFESSOR, PUBLIC HEALTH AND PREVENTIVE MEDICINE; DIRECTOR,
STUDENT HEALTH SERVICE,

AND

B. I. COMROE, M.D.,

ASSOCIATE IN MEDICINE, UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE,
PHILADELPHIA, PA.

(From the Student Health Service, University of Pennsylvania.)

DURING the past 5 years we have observed 64 university students suffering with infectious mononucleosis. Of these, 29 gave positive heterophil-antibody tests. Of the remaining 35, the test was negative in 7 and was not done in the others. This paper is concerned with only the 29 serologically positive cases, 7 of which were treated with sulfathiazole.

It has been our observation that patients with this disease experience rather protracted periods of disability following the subsidence of the acute phase of the illness. The usual procedures employed in management and therapy have proved uniformly disappointing. In view of the infectious nature of the disease, as characterized by onset with sore throat, fever, lymphadenopathy and occasional rash, it was thought that sulfathiazole might be expected to control more effectively the course and duration of the infectious process. We have therefore employed the drug in the treatment of our more recent cases in accordance with the following general plan. An initial dose of 1 gm. of sulfathiazole was given, followed by 0.5 gm. every 4 hours for the first 2 days. Dosage was then reduced to 0.5 gm., 4 times daily, this amount being continued usually for a period of 4 to 8 days. Seven cases received this form of chemotherapy (Table 1, Cases 14, 23, 24, 25, 26, 27 and 29). In the sulfathiazole-treated cases complete blood counts and urinalyses were performed daily and the urinary output was kept above 1200 cc. per 24 hours. Careful hematologic studies are mandatory when using a drug which is capable of producing a leukopenia in a patient in whom the neutrophils are already frequently reduced.

The limited number of patients treated does not warrant a definite appraisal of the value of sulfathiazole in the treatment of infectious mononucleosis. However, the results obtained indicate that it is definitely superior to any form of therapy previously employed in this disease. Clinically, all patients receiving the drug showed definite and prompt improvement. Fever, sore throat, malaise and much of the adenopathy had disappeared after 4 or 5 days. In those patients who did not receive sulfathiazole, the above symptoms persisted for varying periods up to 2 to 4 months, as usually occurs in this disease. Sulfathiazole did not produce any appreciable change in the blood picture in any of the patients in this series. Our previous experience with sulfanilamide in infectious mononucleosis had been disappointing.

Guthrie and Pessel⁵ noted that a transient neutrophilia might appear at the onset of infectious mononucleosis in young adults, with subsequent lymphocytosis which sometimes does not appear until the temperature has returned to normal. Bernstein^{1a} found an increased percentage of neutrophils with a normal total white blood count at the onset in only 1 patient. He believes that blood counts are usually not made until 4 or 5 days after the onset of symptoms and by that time a well-marked lymphocytosis is generally present. In none of our patients did we observe a marked neutrophilia at any time during the course of the disease. However, a normal total white blood count and a normal differential picture was present early in the disease in several patients (Table 1).

The initial white blood count, the count taken on the first day of observation of the patient, was 8000 or less in 44.8% (13) of our

cases (Table 1); in 20.7% (6) it was above 15,000. These counts were all taken within 14 days after the onset of symptoms.

The initial differential picture was essentially normal in 20.7% (6). In 72.4% (21) the percentage of lymphocytes was definitely increased (above 40%) on the initial count and in 55.2% (16) the percentage of neutrophils was decreased (less than 40%).

The highest white blood count encountered in this series was 26,400 (Case 28, Table 1). Much higher counts have been observed; 60,000 (Potter⁷) and 54,500 to 63,000 (Tidy⁸). The lowest count in our series was 3700 (Case 24, Table 1). Bernstein¹⁰ noted white blood counts below 4000 in 7 cases. Others have reported counts as low as 2400 (White¹⁰), 2150 (Blum²), 2000 (Tidy⁸) and 1500 (Davidsohn³). The highest count in our series was taken on the second day after onset of symptoms and the lowest was taken on the fourth day.

TABLE 1.—LEUKOCYTE AND DIFFERENTIAL COUNTS.

Case No.	Name.	Sex.	Age.	Initial count						Day of initial count.
				W.B.C.	P.	L.	M.	E.	B.	
1	W. A. B.	M	22	14.7	24	66	10	11
2	T. N. M.	M	24	11.2	29	66	4	..	1	4
3	K. E. VanB.	M	23	5.6	62	36	2	6
4	G. H. C.	M	23	10.8	41	56	2	1	..	8
5	J. C. G.	M	21	5.6	43	46	1	10	..	7
6	R. F. H.	M	22	4.1	60	35	4	1	..	3
7	W. O. LaM.	M	23	10.1	24	72	4	3
8	W. H. S.	M	23	7.5	52	40	7	1	..	6
9	L. L. T.	M	23	15.8	41	58	1	3
10	E. R. K.	M	24	6.1	45	51	4	2
11	W. H. W.	M	22	11.0	35	57	4	4	..	11
12	J. W. D.	M	21	6.6	52	41	6	1	..	7
13	P. M. Z.	F	21	13.5	24	74	2	1
14.	S. B.	F	19	13.0	17	74	7	2	..	4
15	J. J. Z.	M	25	22.7	27	69	4	14
16	L. W., Jr.	M	22	7.9	56	35	7	2	..	4
17	E. B. W.	M	27	6.9	38	51	7	3	1	3
18	G. A. R.	M	19	18.0	24	66	10	4
19	R. L. H.	M	19	6.2	62	29	4	4	1	2
20	C. R. G.	M	20	16.0	32	65	3	4
21	J. H. F.	M	19	9.0	68	32	1
22	J. R. T.	M	25	6.3	72	25	2	1	..	12
23	R. L. S.	M	22	10.1	27	66	7	7
24	A. W.	M	25	3.7	67	30	3	4
25	R. B. C.	M	22	18.1	27	68	5	4
26	R. J. J.	M	23	7.5	21	71	7	1	..	12
27	C. E. T.	M	22	8.0	23	70	7	7
28	J. D. L.	M	20	26.4	26	62	9	2	1	2
29	R. C. P.	M	22	12.1	28	64	8	3

From our observations there was apparent no definite correlation between the total white blood count and the differential picture; between the total white blood count and the stage of the disease; or between the differential picture and the stage of the disease. The only constant finding was a definite lymphocytosis at some time during the course of the disease.

During the first 2 weeks of symptoms the initial white blood count varied considerably in different individuals. We have seen a normal total white blood count with a normal differential picture; a normal total count with a decrease in percentage of neutrophils and an increase in percentage of lymphocytes; and an increased total count with a decrease in percentage of neutrophils and an increase in percentage of lymphocytes (Table 1). In this series a leukocytosis was encountered in only those cases where the lymphocytes exceeded in percentage the neutrophils.

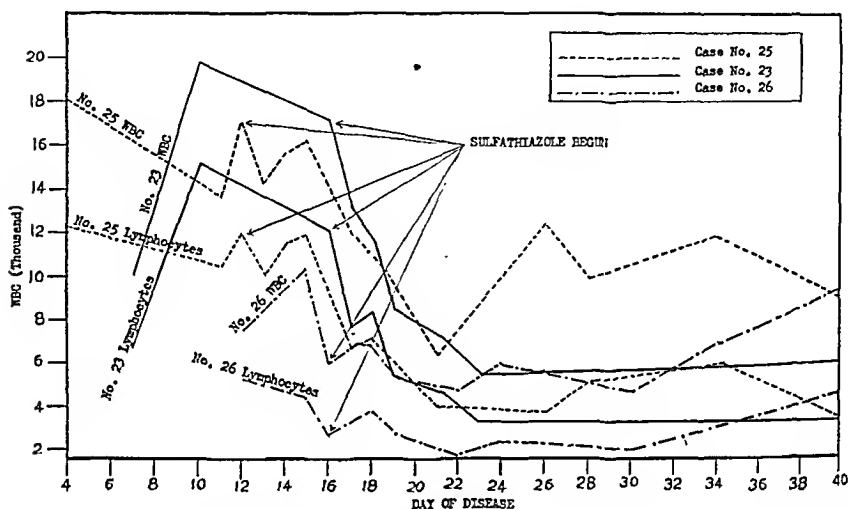


CHART 1.—Total leukocyte counts and number of lymphocytes in three cases treated with sulfathiazole.

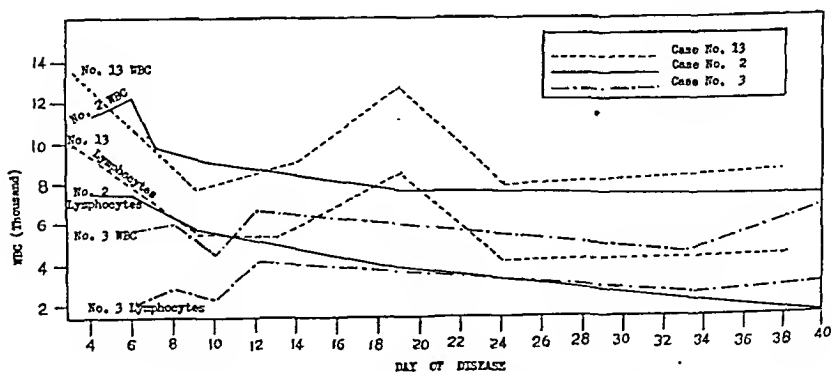


CHART 2.—Total leukocyte counts and number of lymphocytes in three untreated cases.

The symptoms in our 29 cases did not differ from those commonly observed in infectious mononucleosis. The most common and most marked were fever (89.7%), sore throat (72.4%) and general

malaise (72.4%). Less common were headache (41.4%), vague aches and pains (24.1%), tender cervical and axillary nodes (17.2%), chilly sensations and actual chills, nausea and vomiting. Nasal congestion was present in 58.6% (17 cases), acute tonsillitis in 10.3% (3) and Vincent's infection of the gums and pharynx in 6.9% (2). A palpable spleen was present in 31% (9). Cervical lymphadenopathy was noted in 100% (29), axillary in 82.8% (24), and inguinal in 75.9% (22). The usual course of the disease following the acute episode was one of general malaise, ready fatigue, and slight morning or afternoon elevation of temperature for several weeks, persisting in some cases for 4 months or more.

Although the name indicates that the disease is infectious, we have never seen any direct evidence of person to person spread through contact. We have not had more than 1 case from a single fraternity house or dormitory at any one time. Several cases have been present on the campus at the same time, but these usually came from varied student groups having little or no contact with one another. Bernstein^{1b} suggests that the "contagiousness" is low and that the occurrence of sudden outbreaks suggests the possibility of the carrier state. West,⁹ Guthrie and Pessel⁵ and Gooding⁴ have reported epidemics of the disease.

The age group of our patients ranged from 19 to 27 years, this being the age group of the university students with which we come in contact.

Of our 29 cases only 2 (6.9%) were females. However, female students comprise approximately only 13.5% of all cases treated at the Student Health Service. Bernstein^{1b} noted the disease to be more prevalent in the male sex.

Most of our cases occurred in March and in December, 17.2% (5) in each month; 13.8% (4) were seen in February and in May; and 10.3% (3) in January and in April. Since the University is open for only half of June and September, and for none of July or August, we have no figures for these months. West⁹ found no cases in June, July or August, and only 1 in September. He and Bernstein^{1b} each found the highest number of cases in their series in October. Gooding⁴ reported an epidemic in April and May, and Nolan⁶ reported one beginning in November.

In a few of our cases, heterophil-antibody tests done in the first few days of the disease were negative. When the tests were repeated after 1 to 2 weeks, they were found to have become positive. This has suggested the importance of repeating the test during the second week of the disease, as it may not become positive until that time.

Summary. A series of 29 cases of infectious mononucleosis with positive heterophil-antibody tests was studied. Sulfathiazole produced prompt clinical improvement without marked change in the white blood count or differential picture in all 7 of the cases in which it was used.

The heterophil-antibody test was occasionally negative in the first week of the disease and became positive during the second week.

In almost half of the patients the initial blood count was 8000 or less.

ADDENDA. We have seen seven additional patients with infectious mononucleosis since compiling the preceding report. One of these boys, whose initial white blood count was 2000, could not tolerate sulfathiazole because of marked nausea and vomiting. Sulfadiazine was given in one case, but was discontinued because of a resulting high fever and aggravation of symptoms. In five additional cases, sulfathiazole seemed to be of definite value in shortening the symptomatic stage. We have not used convalescent serum in any of these patients.

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AN IMPROVED METHOD OF OBTAINING SUSTAINED CONTROLLED HYPERPYREXIA WITH TRIPLE TYPHOID VACCINE.*

By HARRY A. SOLOMON, M.D.,

CONSULTING PHYSICIAN, U. S. MARINE HOSPITAL, NO. 21; VISITING PHYSICIAN, BELLEVUE HOSPITAL; ATTENDING PHYSICIAN, BETH DAVID HOSPITAL,

AND

EUGENE SOMKIN, M.D.,

ASSISTANT VISITING PHYSICIAN, BELLEVUE HOSPITAL; CLINICAL ASSISTANT PHYSICIAN, MEDICAL OUT-PATIENT DEPARTMENT, MT. SINAI HOSPITAL, NEW YORK CITY, N. Y.

(From the 4th Medical Division, Bellevue Hospital, and the Beth David Hospital.)

WHILE treating cases of subacute bacterial endocarditis with a combination of sulfonamides and hyperpyrexia,¹ the conventional method of obtaining temperature elevations with a single intravenous injection of triple typhoid vaccine† was abandoned in favor of a saline suspension of the organism given by continuous infusion. The temperature elevations obtained by this means have been striking. Periods of hyperpyrexia comparable to those obtained with physical methods were obtained with comparative ease and safety. When one considers the relative costs, space and training required for administration of these two methods, the advantages

* This work was aided by a grant from the Joseph Golding Research Fund.

† 1000 million *B. typhosus* per cc.; 750 million *B. paratyph. A* per cc.; 750 million *B. paratyph. B* per cc.

of this simple technique is apparent, warranting further trial and study.

Method. The patient can be treated in his hospital bed; he must be well covered to minimize heat loss. It is advisable to have a nurse in constant attendance. Triple typhoid vaccine in amounts equal to that ordinarily used in the first of a series of typhoid shock therapy injections is added to 1000 cc. of sterilized normal saline. This is thoroughly mixed and added to the sterilized infusion flask which usually has a capacity of 300 cc. This flask is agitated from time to time to insure an even suspension of organisms. The site of preference for insertion of the needle is a forearm vein. It is important to avoid an arm board, as it restricts the patient's activity and makes the treatment harder to bear. An infusion properly applied gives no difficulty even during the most severe chill. The infusion is started at the slowest rate of flow possible (20 to 25 drops per minute). The chill usually occurs within 35 to 45 minutes, and can be suppressed to a considerable extent by injecting into the infusing tubing at the onset of symptoms, morphine sulphate (.015 gm.) and calcium gluconate or ehloride (1 gm.). If, as occasionally happens, there is no sign of a chill in 45 minutes, the infusion rate may be doubled. From this point on the temperature may be sustained at the effective level of about 104° F. for as long as 6 to 10 hours without further chills. The maximum temperature elevation usually occurs within 1½ hours after the chill. Rectal temperatures every 10 to 15 minutes are quite important at that time. The infusing rate should not be increased by more than 2 times until the temperature has reached a constant level or has begun to fall. At that time the rate of flow may again be doubled or more feasibly an infusing solution with a greater number of killed organisms may be substituted. As a general rule, the longer the temperature has been elevated the greater the number of organisms or drops per minute required to maintain the temperature at 104° F. If the temperature begins to drop before an effective therapeutic period has been approximated, due possibly to a small number of organisms infused during and immediately after the chill, a considerable quantity of organisms may have to be infused within a short period of time to regain previous temperature levels. Another mild chill is the only possible adverse effect of this rapid infusion.

Elevations or depressions in the temperature can be obtained within 10 to 25 minutes by increasing or decreasing the rate of flow. Excessive rises are controlled by sponging, exposing the limbs or antipyretics. Once the infusion is discontinued, the temperature drops rapidly. Replenishing solutions should usually contain twice the number of organisms as the initial solution. Morphine sulphate (.015 gm.) is given intravenously every 3 to 4 hours for restlessness.* In carrying out a series of treatments every day or every other day, the number of organisms used is determined in a manner similar to that of the single injection technique, namely .02 or .03 cc. of triple typhoid vaccine for the first .1, .2, .4 cc. and so on for the succeeding ones.

It is wise to start with a very small number of organisms for the first treatment as there is often a prolonged febrile response and a secondary rise lasting 1 to 2 days. For this reason, we are inclined to feel that since the first injection with its variable response is so often apt to give but a poor temperature elevation, it is simpler to administer only 1 injection of triple typhoid vaccine for the first session. The temperature elevation should be allowed to subside before starting the next treatment. The infusion should not be continued for longer than 6 hours until the febrile responses are properly gauged. As much as 22 cc. of triple typhoid vaccine has been given in an 8-hour session without ill-effects or abnormal tempera-

Several cases of pulmonary suppuration and diffuse fibrosis showed considerable cyanosis, dyspnea and occasional delirium at times. This was rapidly controlled with morphine sulphate (.015 gm.) injected into the infusing tubing. It is important to note that the reactions with this method are quite similar to those of the single injection and usually much less marked.

The therapeutic results with combined therapy will form the subject of another report.

Chart 1 gives a fairly characteristic temperature and pulse curve.

Discussion. The chief drawbacks of hyperpyrexia obtained with a single injection of triple typhoid vaccine are the strenuous chill, the uncertainty of obtaining a suitable temperature rise, the relatively short period of therapeutic fever, the fact that large amounts of the organism must be injected at one time to insure a chill, and the inability to control subsequent course. Attempts have been made to prolong the period of therapeutic fever by giving a doubled dose of triple typhoid vaccine 2 hours after the first.² This results in a second chill and all of the unpleasant symptoms of rapid changes in temperature. Here, too, the hyperpyrexia is rarely sustained over 104° F. for longer than 4 hours. One can obtain a well-controlled and sustained hyperpyrexia by using diathermy and hot box. This method is quite costly, requiring special training in its use. Most small hospitals probably do not have this equipment.

Using the infusion technique we have obtained sustained temperature elevations of over 104° F. from 6 to 10 hours with comparative ease. It never presents more of a risk than the single injection technique, for a certain amount of control is always assured. The characteristic result is one chill which can be controlled. The small number of the organisms actually injected to obtain the chill minimizes the dangers of untoward reactions. Adequate amounts of fluid intake are insured by the continuous infusion; and, should collapse threaten, emergency medication can easily be administered through the infusing tubing. A glucose or saline infusion can be readily substituted for the triple typhoid vaccine suspension. With but little practice in regulating the intravenous drip, one develops facility in maintaining a fairly level temperature curve. This type of heat seems to be borne comparatively well as compared to diathermy and the hot box, probably because there is less stimulation of the skin temperature endings and less dehydration. The contraindications are those of the single injection: namely, intracranial complications, marked debility and cardiac failure. The presence of endogenous fever does not seem to be a contraindication with this method.

Several interesting sidelights on the physiology of triple typhoid vaccine hyperpyrexia have been noted. The prolonged period of hyperpyrexia which can be varied by changing the rate of infusion of organisms without further chills indicates conclusively that mus-

cular contraction plays no rôle in the maintenance, and possibly none in the production of the fever. The very small number of organisms actually used to bring on the chill is also curious, when one considers how the successive doses of triple typhoid vaccine must be multiplied to obtain adequate temperature elevations. On one occasion 20 cc. of the infusion mixture was injected over 20 minutes after which it was discontinued. This represented a small fraction of the number of organisms one would ordinarily use in one injection to obtain a suitable hyperpyrexia. Much to our surprise, the characteristic chill and temperature elevation resulted. A possible explanation for this may be that the mechanism which removes the organism from the blood stream is far more efficient when a large number is injected at one time than with a slow continuous infusion. The prolonged febrile response resulting from the first injection of typhoid organisms, whether in a single injection or infusion, may be of a similar nature: namely, there is no mechanism to remove the organisms from the blood stream and they continue to circulate and give symptoms for 1 to 2 days until they are removed.

The use of protein shock therapy is a rather old and well-established procedure. Its benefits are probably derived from the hyperpyrexia, increased circulation, stimulation of tissue resistance and antibody formation, and the destruction of lymphocytes with liberation of their antibodies. The recent introduction of chemotherapeutic agents has widened the scope of therapy in general. It is but little appreciated how hyperpyrexia can greatly augment the bacteriocidal properties of the sulfonamides^{1,3,4,5} and render effectual a drug which on previous trial had had but little or no effect. This can be carried out with little additional risk to the patient and calls for a reinvestigation of the therapeutic properties of the sulfonamides in other diseases where their use has been discontinued.

Summary. 1. A method for obtaining controlled sustained hyperpyrexia with continuous infusion of triple typhoid vaccine suspensions is described.

2. Using this method in 14 cases for a total of 67 treatments, the temperature was maintained over 104° F. for an average of 4 hours and 20 minutes.

3. It is safe, easy to administer and comparatively economical.

4. The combined use of the sulfonamides and hyperpyrexia offer a therapeutic agent which is far more potent than that of the sulfonamides alone.

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CLINICAL VALUE OF DIGITALIS IN HYPERTENSIVE HEART FAILURE.

I. WITH A NORMAL RATE AND A REGULAR RHYTHM.

BY NATHAN FLAXMAN, M.D.,

CLINICAL ASSOCIATE IN MEDICINE, LOYOLA UNIVERSITY MEDICAL SCHOOL; ASSOCIATE ATTENDING PHYSICIAN, COOK COUNTY HOSPITAL, CHICAGO, ILL.

(From the Department of Medicine, Loyola University School of Medicine, the Columbus Hospital and the Cook County Hospital Service of Dr. Harry J. Isaacs.)

DIGITALIS has a substantial background for its use in heart failure with normal rhythm. The first clinician to indicate this was the younger Janeway.^{3a} In certain cases with normal rhythm he had seen digitalis followed by as speedy relief of symptoms as in fibrillating hearts; this was particularly true in patients with cardiac insufficiency secondary to prolonged high blood pressure.⁶ Pratt⁸ found that digitalis is beneficial in some cases of heart failure with normal rhythm. It was Christian^{1a,b} who noted that even when the heart rate is slow striking digitalis effects may be produced.

Since then the effects of digitalis on the regularly beating heart have been carefully studied and reported. Luten^{7a} stated that the drug exercises an action upon the ventricular muscle which is beneficial independently of any particular cardiac mechanism, and entirely aside from any effect on rate. He added that in administering the drug to patients with normal rhythm it is particularly important to keep clearly in mind the object of therapy, and to appreciate that direct slowing should not be expected; otherwise harmful consequences may ensue. Stewart and his coworkers⁹ administered digitalis to decompensated patients with regular rhythm which resulted in 24 hours in an increased cardiac output, a decrease in cardiac size, a shortening of the circulation time, and a fall in venous pressure if it was elevated. Harrison⁵ stated that the essential action consists in increasing the efficiency of the heart by diminishing dilatation. Evans² emphasized that successful digitalization is best indicated by freedom from symptoms and signs of heart failure, not by actual heart rate. Wood¹⁰ noted that a fall in pulse rate is usually associated with improvement from digitalis therapy, but it is not essential. The drug improves the function of the heart in congestive failure by direct action on the cardiac muscle, which without primary change in the diastolic length of the muscle increases the tension which the muscle can develop in systole.⁴ Many leading clinicians, on the basis of their own experience, have long maintained that the true indication for digitalis has little to do with rate or rhythm.^{7b}

All of the earlier studies on the use of digitalis in heart failure with normal rhythm have included not only cases due to various etiologic factors, but also those with sinus rhythm and sinus tachy-

cardia. Since the etiologic cause of myocardial failure is regarded as very important today, this study is confined to cases with a single etiologic factor. Further, due to the fact that some still question the effects of digitalis on the heart muscle itself, only cases with a regular rhythm whose rate was between 60 and 99 beats per minute are included. Those cases with a rapid, regular rate of 100 to 160 beats per minute are considered in a separate study.³⁴

In a previous report^{3a} on the disturbances of rate and rhythm among 800 cases of uncomplicated hypertensive heart disease, congestive failure with a normal rate and a regular rhythm was noted in 191 patients (23.8%). This was the third largest group among the hypertensive patients; auricular fibrillation, the second largest group, occurred in 198 (24.8%); and the largest were those with sinus tachycardia, which was present in 222 (27.8%). Such a group of patients, representing approximately one-fourth of all cases of hypertensive heart failure, have received little or no attention in the literature. Since it was found that these patients have the lowest mortality of all groups of hypertensives during congestive heart failure, a separate record and analysis was made of all subsequent cases.

Even to one interested in cardiology, patients in congestive failure with normal rate and regular rhythm are the least interesting of all cardiac cases. Such patients have no spectacular symptoms or findings to offer an observer. For this reason it is easy to overlook their failure in the early stages. Aside from the gradual onset with symptoms of dyspnea, and/or precordial or epigastric distress, and palpitation, and the physical findings of an enlarged heart, no other complaints or alterations may be present. Usually, moist râles are present at the bases of the lungs with isolated failure of the left ventricle; while with the combined left- and right-sided failure, in addition to the râles, an enlarged tender liver and edema are found. Seldom does the onset occur abruptly with such alarming symptoms as paroxysmal nocturnal orthopnea, cardiac asthma, or Cheyne-Stokes respiration.

TABLE 1.—DISTRIBUTION OF CASES ACCORDING TO AGE.

Age groups.	Male.	Female.	Total.	%.
25-30	1	0	1	0.7
31-40	5	0	5	3.1
41-50	40	12	52	32.5
51-60	65	8	73	45.6
61-69	23	6	29	18.1
Totals	134	26	160	100.0

The material in this study is based on the clinical analysis of 160 cases of hypertensive heart failure who had a normal rate and a regular rhythm at the onset and during the congestive failure. They were seen in succession, and selected only in the sense that each had the heart failure on the basis of essential hypertension; 83%

were males and 17% were females. The ages varied from 25 to 69 years (Table 1); 78.1% were in the hypertensive age of 40 to 60 years. Among all hypertensives 78.8% were in the same age group,^{3b} while in 158 with auricular fibrillation 77.1% were in the same ages.^{3c}

Duration of Symptoms in Relation to the Outcome. As far as could be personally determined, all of the patients were in their first decompensation. Many of them had been under observation at one time or another for a variety of ailments. About one-third had the psychoneurotic complaints of headache, dizziness, tinnitus, and 23 other similar symptoms.* Regardless of the duration of the symptoms before treatment with digitalis was started, the prognosis was the same (Table 2). The majority, 82 (51%), had the symptoms less than 4 months.

TABLE 2.—DURATION OF CARDIAC SYMPTOMS IN RELATION TO THE MORTALITY.

Duration.	Cases.	Deaths.	Mortality (%)
Less than 1 mo.	39	9	23
1-2 mos.	22	5	22.7
2-4 "	21	6	28
4-6 "	19	5	26
6 mos.-1 yr.	18	5	26
Over 1 yr.	41	7	17
Totals	160	37	23

Type of Heart Failure. There are three types of hypertensive heart failure: 1, the combined right- and left-sided ventricular failure, denoted by symptoms of dyspnea alone or associated with cardiac pain, palpitation, or weakness, with the signs of systemic congestion; 2, isolated failure of the left ventricle, denoted by symptoms of dyspnea or cardiac pain alone or by dyspnea associated cardiac pain, palpitation, or weakness, and no signs of systemic congestion; and 3, isolated failure of the right ventricle, denoted by the symptom of epigastric pain usually, and with signs of systemic congestion.^{3d} Among all types of hypertensives the combined type of failure was noted in 72.5% and left ventricular failure in 26.5%.^{3d} In the present series of 160 cases the incidence was 66.8% and 33.2%, respectively. The type of hypertensive heart failure has prognostic significance, but in this study the difference in mortality was not as marked. Of those with combined failure, 27 (25%) died, as compared with 10 (18%) of those with isolated failure of the left ventricle (Table 3).

TABLE 3.—TYPES OF HYPERTENSIVE HEART FAILURE IN RELATION TO MORTALITY

Type.	Cases.	Deaths.	Mortality (%)
Combined ventricular	107	27	25
Left ventricular	53	10	18

* Unpublished data.

Duration of Decompensation. The length of time required to restore compensation in these patients seems to have an influence on the outcome. From Table 4 it is noted that the longer the decompensation persisted after treatment with digitalis was begun, the greater the average mortality. Fatalities were heaviest among those whose myocardial failure persisted 6 weeks or longer after treatment commenced.

TABLE 4.—DURATION OF DECOMPENSATION IN RELATION TO MORTALITY.*

Duration.	Cases.	Deaths.	Mortality (%)
Less than 2 wks.	79	12	15
3 wks.	30	6	20
4 "	24	6	25
6 "	13	4	30
8 "	5	3	60
12 "	6	4	66
16 "	3	2	66

* After treatment with digitalis has started.

Causes of Death. Uremia, the important cause of death among these patients, was responsible for 19 (51%) of the 37 deaths during treatment. This is a factor which cannot be controlled by digitalis or by any other type of therapy at the present time. Regardless of the type of failure, it was still the common cause of death (Table 5). Ranking second in importance were congestive heart failure, especially among those with the combined type, and coronary thrombosis, in those with failure of the left ventricle. The frequency and importance of coronary thrombosis occurring during isolated failure of the left ventricle due to essential hypertension has received the special attention it merits.^{3e}

TABLE 5.—CAUSES OF DEATH IN 37 CASES OF HYPERTENSIVE HEART FAILURE WITH NORMAL RATE AND REGULAR RHYTHM.

Cause of death.	Combined ventricular failure.		Left ventricular failure.		Total.	%
	Cases.	%.	Cases.	%.		
Uremia	13	48.0	6	60.0	19	51.0
Congestive heart failure	12	44.4	1	10.0	13	35.0
Coronary thrombosis	1	3.8	3	30.0	4	10.3
Cerebral hemorrhage	1	3.8	1	2.7

Case Reports. CASE 120. N. C., a 50-year-old male laborer, complained of dyspnea, cough, and palpitation of 3 months' duration. The symptoms had a gradual onset and increased in severity, especially during the last week. He was a known hypertensive, having been originally seen 1 year before at which time a blood pressure of 190/110 and a transverse cardiac measurement of 16 cm. were noted. On this last occasion the physical examination revealed a blood pressure of 210/130, impaired resonance and moist râles over both lung bases, a transverse cardiac measurement of 19 cm., a soft systolic murmur at the apex, and an accentuated second aortic sound. The liver was not palpable and no edema was present. There was a trace of albumin in the urine. The blood urea nitrogen was 38, and the creatinine was 2. He was already on bed-rest, and digitalis, along with sedatives, were given. Three days after treatment was begun

he appeared very drowsy and incoherent. The blood chemistry showed a rise in the urea nitrogen to 62.1 and the creatinine to 6. Although he was digitalized and the failure of the left ventricular cleared, the uremic manifestations increased. Eleven days after treatment was started the urea nitrogen was 120 and the creatinine 9. He expired in terminal uremia 18 days after first being seen for the failure of the left ventricle. An autopsy revealed an eccentric hypertrophy of the heart (620 gm.), arterio-sclerotic contracted kidneys with granulation, passive congestion of the liver and lungs, and atherosclerosis of the aorta.

This case is illustrative of the outstanding uncontrollable factor in the course of hypertensive heart failure with a normal rate and a regular rhythm. In spite of a good cardiac response to digitalis, the patient died in uremia.

CASE 40.—M. W., a 54-year-old male clerk, complained of dyspnea and precordial pain of 6 months' duration. He was known to have high blood pressure over 6 years, and during those years it varied from 160/90 to 170/110 and the transverse cardiac measurement increased from 14 to 18 cm. On this last occasion the physical examination revealed a blood pressure of 150/96, moist râles at the bases of both lungs, and a transverse cardiac measurement of 22 cm. The liver was not palpable and no edema was present. The urine contained a trace of albumin, and the blood urea nitrogen was 17. An electrocardiogram showed a rate of 86, notching and slurring of the QRS complexes, and negative T waves in Leads 2 and 3. He seemed to respond well to digitalis as the dyspnea and pain diminished and the râles cleared. On the third day after treatment was started he suffered a severe attack of acute coronary artery thrombosis while still in bed. He lingered for 9 days, and expired 12 days after treatment was commenced. An autopsy revealed severe sclerosis of the coronary artery with marked narrowing of the lumen, a recent thrombus occluding the left descending branch of the coronary artery at the site of an atheromatous ulcer, scarring and recent myomalacia in the anterior wall of the left ventricle, marked eccentric hypertrophy of the heart (880 gm.), edema of the lungs, atherosclerosis of the aorta and splenic arteries, chronic passive congestion of the liver, spleen, kidneys, arterio- and arteriolosclerosis of the kidneys.

This case illustrates another uncontrollable outcome in the course of hypertensive heart failure. In spite of what appeared to be a good response to digitalis, death was due to an acute coronary artery thrombosis which occurred on the third day after treatment was started.

CASE 64.—H. W., a 54-year-old salesman, was a known hypertensive of 5 years' duration. His blood pressure had varied from 200/120 to 280/150 and the transverse cardiac measurement was 15 cm. On this last occasion, when he complained of dyspnea and nocturia of 6 weeks' duration, the physical examination revealed a blood pressure of 290/150, moist râles at the bases of both lungs, a transverse cardiac measurement of 19 cm., and a booming aortic second sound. The liver was not palpable, and no edema was present. There was a moderate amount of albumin in the urine, and the blood urea nitrogen was 17. Digitalis therapy was instituted. In the midst of what appeared to be a favorable response, he suddenly and very unexpectedly expired while sitting up in bed. His death occurred on the fourth day after treatment was begun. An autopsy revealed marked eccentric hypertrophy of the heart (570 gm.), moderate sclerosis of the coronary arteries, arteriosclerosis of the kidneys, edema of the lungs, and chronic passive congestion of the liver and spleen.

This case might be taken as a failure of response to digitalis, but aside from the evidence of congestive heart failure at autopsy no other factor could account for the sudden death on the fourth day of treatment. Among the 160 cases in this series there was one other sudden cardiac death. This

was in a 50-year-old male, decompensated 2 months, who suddenly expired on the eighth day of treatment when the gross signs of congestive heart failure had already disappeared. An autopsy was not obtainable, and the cause of death, although assumed to be congestive heart failure, was not clear.

Comment. In spite of these unavoidable deaths, a small number of patients with hypertensive heart disease lived 10 to 20 years after the onset of cardiac symptoms.³⁷ Considering the large groups of hypertensive patients, those with a normal rate and a regular rhythm have a good prognosis. And those with failure of the left ventricle have a better outlook than those with the combined type of failure.

What the relationship is between the normal rate and the high incidence of uremic deaths, if any does exist, is a question which remains to be explained. It is entirely possible that passive congestion and edema of the kidneys alone are sufficient to interfere with the extraction and filtration of the end-products of nitrogen metabolism. However, it is the force and not the frequency of the heart stroke, working on the principle of a pump, that maintains an adequate circulation. When the force of each beat fails to convey the blood properly, the beats usually increase and a tachycardia further goads the already laboring heart on to failure. In these cases with a normal rate, only the force of the stroke is decreased and for some unexplainable reason an increase in rate does not occur. As long as the rate is normal the blood supply to the heart muscle itself remains adequate. In all other cases of hypertensive heart failure, especially those with sinus tachycardia or auricular fibrillation, the main cause of death is congestive heart failure. Although it may not explain why the rate remains normal, it is possible to assume the following: when the rate is normal, there is no interference with the blood supply to the heart itself; therefore, the heart muscle does not develop any anoxic areas which lead to a more rapid rate, regular or irregular, in the struggle to bring more blood, and with it more oxygen, to the suffocating hypertrophied heart muscle.

Finally, the question is often raised as to whether digitalis is really needed to reestablish compensation in heart failure with normal rhythm. Such an interrogation may be answered simply. A few decompensated patients with normal rhythm recover without any digitalis, and a few die in spite of adequate digitalis therapy, but in the main the drug reestablishes compensation and returns to usefulness at least 77% of the hypertensive heart failures with a normal rate and a regular rhythm.

Summary. 1. The study of 160 cases of hypertensive heart failure with a normal rate and a regular rhythm is reported.

2. The age of the patient and the duration of the symptoms before treatment with digitalis apparently had no influence on the outcome.

3. Of all the hypertensive patients who develop congestive heart failure, those with isolated failure of the left ventricle, a normal heart rate, and a regular rhythm have the best prognosis.

4. Factors over which digitalis itself had no control, such as uremia, coronary thrombosis, and cerebral hemorrhage, caused 22 (64%) of the 37 deaths in this series of 160 cases.

5. Treatment with digitalis may be regarded as most successful in these decompensated hypertensive patients, despite the normal rate and the regular rhythm.

The digitalis preparations used in this study were generously supplied by Parke, Davis & Co., and Ciba Pharmaceutical Products, Inc.

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CLINICAL VALUE OF DIGITALIS IN HYPERTENSIVE HEART FAILURE.

II. WITH SINUS TACHYCARDIA.

BY NATHAN FLAXMAN, M.D.,

CLINICAL ASSOCIATE IN MEDICINE, LOYOLA UNIVERSITY MEDICAL SCHOOL; ASSOCIATE ATTENDING PHYSICIAN, COOK COUNTY HOSPITAL, CHICAGO, ILL.

(From the Department of Medicine, Loyola University School of Medicine, the Columbus Hospital and the Cook County Hospital Service of Dr. Harry J. Isaacs.)

AMONG hypertensive patients who develop heart failure, the largest group is composed of those who have a rapid, regular cardiac rate of 100 to 160 beats per minute.^{2a} Such cases constitute approximately 28% of all hypertensive heart failures, followed by auricular fibrillation in 25%, and a normal sinus rhythm in 24%. The mortality among these hypertensives with sinus tachycardia was 39.2%.^{2a} Except for those with A-V nodal rhythm,^{2b} which has a mortality of 50%, the hypertensives with a rapid, regular rhythm have the highest fatality rate. It was 20% higher than the mor-

tality among the hypertensive heart failures with a normal, regular rate of 60 to 99 beats per minute.

The symptoms of the majority of these patients have an alarming onset. Usually, an upper respiratory infection, followed by a cough of a week to 10 days' duration, precipitated the acute onset of dyspnea and precordial distress. It was not unusual to have such a hypertensive patient walk slowly into the office, considerably unnerved because of the rapid onset of dyspnea within a short period of time. In addition to the dyspnea and precordial or epigastric distress, many complained also of palpitation and weakness. Frequently the onset came abruptly at night, or following a heavy evening meal, and was characterized by an attack of paroxysmal nocturnal dyspnea, or cardiac asthma, or Cheyne-Stokes respiration.

Physical examination in these hypertensives revealed an enlarged, rapidly beating heart, a rapid regular pulse, and fluid in the lungs, ranging from crepitant râles in one or both bases to acute pulmonary edema, depending on the rapidity and severity of the myocardial failure. This abruptness of failure of the left ventricle appeared extremely serious. If the right side of the heart failed, and it followed shortly after the failure or occurred at the same time in 72.5% of the patients, then an enlarged liver and edema became apparent. Such an alarming onset was in contrast to that of hypertensive heart failure with a normal rate and a regular rhythm, where the symptoms appeared gradually, and the sudden, severe manifestations of myocardial insufficiency were uncommon.^{2c}

Because of the differences not only in the onset but also in the rate, this study is based on the analysis of 160 cases of hypertensive heart failure with rapid, regular rhythm. Of this group, 72% were males and 28% were females. Their ages varied from 31 to 67 years (Table 1), and 77.9% were in the hypertensive age of 40 to 60 years. Among all hypertensive patients 78.8% were in the same age groups;^{2d} among those with a normal sinus rhythm, 78.1%;^{2c} and in 158 cases with auricular fibrillation, 77.1%.^{2e}

TABLE 1.—DISTRIBUTION OF CASES ACCORDING TO AGE AND SEX.

Ages.	Male.	Female.	Total.	%.
31-40	16	5	21	14.1
41-50	42	24	66	41.1
51-60	46	13	59	36.8
61-67	11	3	14	8.0
Totals	115	45	160	100.0

Duration of Symptoms in Relation to Outcome. Many had been under observation or treatment because of the essential hypertension or other conditions. However, in regard to the duration of symptoms before treatment was started, the mortality did not vary enough to be of any significance (Table 2).

TABLE 2.—DURATION OF SYMPTOMS IN RELATION TO THE MORTALITY.

Duration.	No. of cases.	Mortality (%)
1 mo. or less	40	27.5
1 to 2 mos.	31	32.0
2 to 4 "	11	27.0
4 to 6 "	18	33.0
6 mos. to 1 yr.	30	40.0
1 to 2 yrs.	13	30.0
2 to 5 yrs.	13	23.0
Over 5 yrs.	4	0.0
Totals	160	30.0

Type of Heart Failure. The type of hypertensive heart failure has been shown to have prognostic value.^{2f} In this study, where the combined type of right- and left-sided ventricular failure occurred in 72.5% and isolated failure of the left ventricle in 27.5%, it was very apparent. Table 3 indicates that 44 (37.7%) of the 116 patients with combined failure died, while in the 44 with failure of the left side only 5 (11.3%) expired while under treatment.

TABLE 3.—TYPES OF HEART FAILURE IN RELATION TO THE MORTALITY.

Type.	Incidence (%)	Cases.	Deaths.	Mortality (%)
Combined	72.5	116	44	37.7
Left	27.5	44	5	11.3
Totals	100.0	160	49	30.0

Duration of Decompensation. The length of time required to re-establish compensation in these patients appeared to influence the prognosis. Up to 6 weeks after treatment with digitalis was started, the mortality was about the same (Table 4). After that period, if the decompensation still persisted in spite of adequate treatment, the prognosis became increasingly worse.

TABLE 4.—DURATION OF DECOMPENSATION AFTER BEGINNING DIGITALIS IN RELATION TO THE MORTALITY.

Duration.	No. of cases.	Mortality (%)
2 wks. or less	73	26.0
3 "	23	26.0
4 "	23	26.0
6 "	15	27.0
8 "	12	39.0
12 "	6	50.0
16 "	7	71.0
20 "	1	100.0

Causes of Death. Congestive heart failure was the common cause of death (Table 5). All of the deaths due to this controllable factor occurred in patients who had the combined type of failure on presentation. Many of them had apparently dissipated the major portion of their cardiac reserve before the alarming symptoms came on so

abruptly. Uremia (12%) was second in importance, and coronary thrombosis (10%) was third. Singularly, not only was the mortality isolated failure of the left ventricle, but none of these 5 deaths, much less, but none of the 5 deaths were due to congestive heart failure. Coronary thrombosis, which caused 4 of these 5 deaths, had an incidence of 20% among the 44 cases of failure of the left ventricle. This has been emphasized on several occasions.^{2,5} There were no sudden, unexpected deaths among these 160 cases of hypertensive heart failure with sinus tachycardia.

TABLE 5.—CAUSES OF DEATH IN 49 CASES.

DEATH IN 49 CASES.					
Causes.	Type of hypertensive heart failure.				
	Combined.		Left.		Total (%).
	Cases.	%.	Cases.	%.	
Congestive heart failure	34	77.0	69.0
Uremia	6	13.0	12.0
Coronary thrombosis	1	2.5	10.0
Cerebral hemorrhage	2	5.0	4	80.0	4.5
Miscellaneous	1	2.5	4.5
Totals	44	100.0	5	100.0	100.0

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Comment. The relationship of tachycardia to heart failure is difficult to determine. It is not unlikely that in many instances the tachycardia precedes and precipitates the heart failure. This has been shown to occur in auricular fibrillation where the arrhythmia was the first sign, and because of the rapid rate, evidence of myocardial insufficiency appeared in a few days.^{2a,c} Luten^{6a} stated that the tachycardia which occurs in heart failure is a compensatory mechanism secondary to, and not the cause of, the failure. An opposing view is that the tachycardia often develops in the presence of a hypertrophic heart and usually brings on premature failure.⁶ During diastole the left ventricle receives its blood supply, and an increase in heart rate interferes with the oxygenation of the cardiac muscle fibers. The tachycardia not only goads the weak muscle to more frequent contractions but deprives the harassed myocardium of adequate nourishment.

In general, among all cases of this etiology, those with a sinus tachycardia have the worse prognosis, excepting A-V nodal rhythm. The rapid rate, caused by infection or exertion or a combination of both, decreased the cardiac reserve and brought on the heart failure. The hypertensive patient in this group stands a better chance of recovery, for congestive heart failure, the common cause of death, is a controllable factor if treated early and adequately. Yet in spite of the alarming symptoms that many of these patients had at the onset of myocardial failure, they did not seek medical attention any sooner than those who had a normal rate and a gradual onset. Some explained that they had had previous attacks but they got over them until this one came along. Perhaps the con-

tinned disregard of such ominous signs of heart failure accounts for the high mortality.

The essential drug used in these cases, digitalis, exercises an action upon the ventricular muscle which is beneficial independently of any particular cardiac mechanism, and altogether aside from any effect on rate.^{5b} When the drug is administered to these patients with normal rhythm it is especially important to keep clearly in mind the object of therapy, which is the reestablishment and maintenance of compensation. Direct slowing of the cardiac rate should not be the goal or harmful consequences may ensue. Successful digitalization is best indicated by freedom from symptoms and signs of heart failure, not by the actual cardiac rate.³ Although a fall in pulse rate is usually associated with improvement from digitalis therapy, it is not essential.¹ When the cardiac rhythm is regular the fact that the rate is rapid is no proof that the heart can stand more digitalis. In some cases the question whether more or less digitalis is needed is one that can be ascertained only through trial and error, for the main point is whether the clinical condition improves with one type of regimen or another.⁴

Summary. 1. The study of 160 cases of hypertensive heart failure with sinus tachycardia is reported.

2. The cardiac rate is important as a prognostic sign, because the mortality among these patients, with the exception of A-V nodal rhythm, was the highest of all groups of hypertensives.

3. Exempted were those with isolated failure of the left ventricle where the mortality, due chiefly to coronary thrombosis, was only 11.3%, as compared with a mortality of 37.7% among those with the combined type of ventricular failure.

4. Congestive heart failure, the factor controllable by digitalis, was responsible for 34 (69%) of the 49 deaths, but all of these were in patients who had the combined type of failure before the treatment was started.

5. Digitalis was administered to these hypertensive patients with rapid, regular cardiac rhythm not for its action on the rate, but to relieve the symptoms and signs of heart failure, which it did successfully in 70% of the patients.

The digitalis preparations used in this study were generously supplied by the Ciba Pharmaceutical Products, Inc., and Parke, Davis & Co.

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BOOK REVIEWS AND NOTICES

CLINICAL HEMATOLOGY. By MAXWELL M. WINTROBE, M.D., PH.D., Associate in Medicine, Johns Hopkins University; Associate Physician, Johns Hopkins Hospital, and Physician-in-Charge, Clinic for Nutritional, Gastro-Intestinal and Hemopoietic Disorders, Baltimore. Pp. 792; 167 illustrations and 7 colored plates. Philadelphia: Lea & Febiger, 1942. Price, \$10.00.

THE author, one of the acknowledged leaders in hematology in this country, offers an accurate, carefully prepared treatise on a subject that has received many important additions in recent years. In achieving his goal of a systematic presentation that sifts the more from the less important, he details the best of the new methods, gives a guide to differential diagnosis and treatment, and yet finds space to clarify the fundamental nature of the disease processes concerned. The information is organized from "thousands of publications," 2400 of which are referred to at the ends of the various chapters.

One naturally finds some items that seem capable of improvement: among them, for instance, the concept of the placental origin of erythroblastosis fetalis should have been given; especially in war time, one would have liked to have found mustard gas included as a cause of leukopenia; Minot's Nobel prize-winning achievement in removing pernicious anemia from among the uniformly fatal diseases is surprisingly underemphasized; Feitis' Fleckmilz might have received brief notice. The author has maintained such marked reserve in the complex field of the lymphomatoid diseases, and so many types are considered, at least in part under common headings, that attainable clearness is not attained.

A novel arrangement of the various sections devoted to each disease reserves "Pathology" (really "Pathologic Anatomy") and "Pathogenesis" as the last items—more suggestive of their position in single case studies than of an orderly consideration of the disease process. Many will find the Appendix on comparative hematologic data and references very useful. The format is excellent. The illustrations, which include camera lucida drawings and photographs of living blood cells, really illustrate, and we have found very few typographical errors.

We believe that the author has well performed the difficult task of making a valuable contribution to a specialty that in recent years has been unusually well supplied with good textbooks. We know of no better book in its field.

E. K.

METHODS OF TREATMENT IN POSTENCEPHALITIC PARKINSONISM. By HENRY D. VON WITZLEBEN, Elgin State Hospital, Elgin, Illinois. Preface by THEODORE J. C. VON STORCH, Associate Professor of Neurology, Albany Medical College; Attending Neurologist, Albany Hospital. Pp. 164. New York; Grune & Stratton, 1942. Price, \$2.75.

This monograph, on a devastating disease, is by an authority of much experience. In this country, the number suffering from the affection is probably more than 60,000. "Hassler has clearly demonstrated that in most postencephalitic Parkinsonism all groups of cells in the substantia nigra are altered. . . . tremor is due to changes in the anterior part, while

the rigidity is caused by lesions in the posterior part." Three forms of Parkinsonism must be differentiated: postencephalitic, arteriosclerotic, and paralysis agitans.

The author recognizes the following as characteristic of the postencephalitic form: an acute stage of epidemic encephalitis; intensive akinesia and deficiency of mimic and reactive movements; frequent absence of tremor; absence or infrequent appearance of pill rolling; salivation; oily skin; supplementary complications, such as paresis of eye muscles, oculogyric crisis; sleepiness or sleeplessness; more pronounced motor disorders than in paralysis agitans; remarkable improvement with the Bulgarian treatment.

History of the Bulgarian treatment of this disease touches romance. Some 15 years ago, continental Europe was surprised at rumors telling of successes obtained with the secret remedy employed by a layman, named Raeff. Then, through research work inspired by the Queen of Italy, the product and its method of use were revealed.

After considering the other methods of treatment, the writer describes the use of his remedy, "Bulgkaur," which is a standardized total extract from the Bulgarian belladonna root, of proper age and gathered at the proper time. As a rule, treatment is begun with a drop a day, and is increased to from 15 to 25 drops, 3 times a day. Patients showing rigidity usually require larger doses than subjects with tremor. The side effects are similar to those of atropine, but appear later and are milder. An important adjunct to treatment includes physical exercises, massage, calisthenics, the use of splints, and so on. The course is long, difficult, and calls for the utmost patience on the part of both subject and instructor. There are numerous contraindications.

Gratified with the results of his treatment, the author tells of long bed-ridden subjects displaying marked improvement; and from the social viewpoint of his 837 patients, "71 per cent of all cases succeeded in returning to work." The bibliography covers more than 23 pages. N. Y.

LABORATORY DIAGNOSIS OF PROTOZOAN DISEASES. By CHARLES FRANKLIN CRAIG, M.D., M.A. (HOB.), F.A.C.S., F.A.C.P., Colonel, United States Army Medical Corps, Retired. D.S.M. Emeritus Professor of Tropical Medicine, Medical School, Tulane University, etc. Pp. 349; 54 illustrations, and 4 colored plates. Philadelphia: Lea & Febiger, 1942. Price, \$4.50.

This book adequately describes all forms of protozoa that are parasites of man, and gives detailed instructions for collecting and examining feces, blood, cerebrospinal fluid and tissues for these organisms. Staining methods, cultivation and animal inoculation also receive careful attention. A considerable bibliography, over 8 pages, is appended. Subjects and authors are indexed separately. The author has given a large part of an active life to the study of parasitic diseases, especially those due to protozoa. No one is better fitted to compile this critical review of the various laboratory methods that have been advocated for the diagnosis of protozoan infections.

H. R.

WILLIAM HENRY WELCH AND THE HEROIC AGE OF AMERICAN MEDICINE. By SIMON FLEXNER and JAMES THOMAS FLEXNER. Pp. 539; illustrated. New York: The Viking Press, 1941. Price, \$3.75.

This book may be read with equal interest and enjoyment by laymen and doctors. It is the story of a great American and of a great epoch. No man has more profoundly influenced American medicine than Dr. William Henry Welch, the "Popsy Welch" of Hopkins who became a legend while still hale and hearty.

The story tells of Dr. Welch's New England ancestry—a long line of doctors—and of his childhood in the pleasant Connecticut town of Norfolk, which as he wrote many years later “afforded the best this country could offer in the way of heredity and environment for the upbuilding of that strength of character, that soundness of mind and of body, those moral and intellectual ideals which have been in the past (whatever the future may have in store for us) the determining forces in the development and prosperity of our country.” When he was sixteen, he went to Yale—a college still walking in its ancient ways, a very different Yale from the great University of today—where he received virtually no instruction in science but where he fell under the spell of the classics; his aspiration at the time of his graduation was to be called back as a tutor of Greek. His conversion to medicine came slowly; after another year at Yale studying chemistry (surely an almost intuitive choice in those days), he left New Haven when 22 years old and entered the College of Physicians and Surgeons in New York. Here he met inspiring teachers; Dr. Welch in later years attributed the “flowering of his interest in medicine not so much to the studies he pursued as to the personality of his teachers.” There are many early indications that his interests were directed not toward the practice of medicine but toward a career in the medical sciences. By the time he had reached the age of 25 he was sure that he wanted to become a professor of pathologic anatomy and devote all of his time to teaching and research (such a position, be it remembered, did not then exist in America). Soon afterward he went abroad to study. He was fortunate in the choice of his teachers who, investigators of the first rank themselves, imbued him with the spirit of research. Perhaps he owed most to Julius Cohnheim, for in his laboratory he learned the application of the methods of physiology to the problems of pathology. Now came years of struggle and disappointment in New York, where he established at Bellevue Hospital the first laboratory of established Johns Hopkins Medical School. Here he became the first member of the faculty of the new school, himself choosing the designation of the chair as “Professorship of Pathology” (instead of, as was then customary, professorship of morbid anatomy, or of pathologic anatomy or of general pathology and like terms). His choice was at the time unprecedented; but it denoted his concept of a pathology which was to cover “the whole broad field of the origin and nature of disease,” the science of disease in its entirety. Followed happy years in the laboratory, training assistant-teaching students, doing experimental research. But he also helped in the organization of the school and he assumed the burden of deanship. He founded, and edited for some years, the *Journal of Experimental Medicine*, the first journal in this country devoted purely to the scientific investigation of medical problems. The success of the journal testified at once to the new spirit of inquiry in this country; that the journal survived and today is one of the world's foremost is proof that the awakening was not ephemeral. Of importance equal to the creation of a journal for the dissemination of scientific knowledge was the creation of an institute solely dedicated to the acquisition of knowledge; namely, the founding of The Rockefeller Institute for Medical Research. Dr. Welch's part in the planning of the Institute, and in the fortunate choice of his first Director—the senior author of this biography—was dominant. But all of these activities took him from his laboratory, and his research. Dr. Welch's genius for organization was now so well recognized that he had inevitably become more and more an administrator and public servant, “our greatest statesman in the field of public health,” as the President of this country called him on his 80th birthday. There is much temptation to linger over the writing of this review and speak further of this man who to the generation now ageing was a great symbol. But at best the Reviewer can but spoil the better word picture

which the Flexners, father and son, have given in their book. To those who had not known Dr. Welch in the flesh, there will take form, as the pages are turned, a friendly, tolerant, genial, fun-loving, very human, learned and wise man to whom we all owe much; and those who were so fortunate as to have known Dr. Welch, however, slightly, will love him the more for this story.

B. L.

PSYCHIATRY IN MEDICAL EDUCATION. By FRANKLIN G. EBAUGH, M.D., Professor of Psychiatry, University of Colorado School of Medicine; Director, Colorado Psychopathic Hospital, and Division of Psychiatric Education, National Committee for Mental Hygiene, and CHARLES A. RYMER, M.D., Associate Professor of Psychiatry, University of Colorado School of Medicine; Assistant Director, Colorado Psychopathic Hospital. Pp. 619; illustrated. New York: The Commonwealth Fund, 1942. Price, \$3.50.

THERE is discussion in this book that can be valuable to any dean or any teacher who is engaged in fitting a medical curriculum to students' needs. In its examination of the failures and successes of psychiatric teaching it reaches medical education in general.

The material consists of the records of a survey of 68 medical schools in 1932 and questionnaires which have brought these records up to date. The authors have given this material good editing but also have put in their own personal experience, judgment and suggestions so that the book has life.

Premedical college work gets little praise, because of its failure to give the student a conception of a patient who is always affected by the society about him—of a patient who is a person. There is a downright denunciation of courses in abnormal psychology in colleges.

In the medical schools the authors discuss departmentalism, the selection of medical students, teaching techniques, the general situation of the students, the fact that a medical faculty "abhors a vacant hour in the curriculum as nature abhors a vacuum."

Even the chapters on the teaching of psychiatry have a general interest because they give the opinions of surgeons, internists, pediatricians and students about the place of psychiatry and because liaison with other medical teaching is emphasized. The authors see the teaching and clinical facilities of psychiatry as often inadequate, and they divide the blame fairly. There is a full discussion of psychiatry in the general hospital.

E. B.

THE DOCTORS MAYO. By HELEN CLAPESATTLE. Pp. 822; illustrated. Minneapolis: The University of Minnesota Press, 1941. Price, \$3.75.

NEVER in the history of this country, perhaps even of the world, have two brothers, starting so modestly, attained such proficiency and prominence in the medical profession and collaborated in using this prominence so constructively in forwarding medical science and practice. The story of such a remarkable achievement is necessarily an enthralling one, and Miss Clapesattle, the historian and editor of the Minnesota Press, has made good use of the free access she has had to a rich source material.

From the time that William Worrall Mayo, "The Old Doctor," left England in 1845, to the death of his more famous sons—within 2 months of each other—in 1939, the family story is unrolled—the father's pharyngeal days at Bellevue, his pioneer and Civil War days in New York, his death in Rochester, the cyclone of 1883 that brought together the two brothers, the doctor and the internist, the recognition, and the Foundation that ensured co-operation of the two training center for future generations. Each

his own field, the brothers were among the first to realize the importance of coöperation in medicine and were successful in gathering good men to work with them. It is the brothers who dominate the book, however, and the human touch with them has been preserved with frequent glimpses of personal characteristics and anecdotes.

The illustrations would illustrate better if they were not rather awkwardly gathered into four groups, presumably for binding purposes. The study is unusually well documented with 83 pages of bibliographic notes and is adequately indexed. It has obviously been prepared with great care; and yet, perhaps because of the tremendous prepublication publicity by advertisement, colored postcards and news releases, one lays it down without the feeling of satisfaction that had been anticipated. It is a praiseworthy but not a great biography; and more valuable as an authoritative record than as an entertaining story. But how often should one expect a Cushing's "Book" in one generation?

E. K.

THE BLOOD BANK AND THE TECHNIQUE AND THERAPEUTICS OF TRANSFUSIONS. By ROBERT A. KILDUFFE, A.B., A.M., M.D., F.A.S.C.P., Director, Laboratories, Atlantic City Hospital; City Bacteriologist, Atlantic City; Serologist, Municipal Hospital for Contagious Diseases, Atlantic City; etc., and MICHAEL DEBAKEY, B.S., M.D., M.S., F.A.C.S., Assistant Professor of Surgery, School of Medicine, Tulane University of Louisiana; Visiting Surgeon, Charity Hospital, Touro Infirmary, and Mercy Hospital, New Orleans, etc. Pp. 558; 214 illustrations. St. Louis: The C. V. Mosby Company, 1942. Price, \$7.50.

This book covers the entire field of transfusion, including the most recent innovations, such as the use of plasma and serum. The search of original sources has been most thorough, and the bibliography itself is very valuable. This presentation has avoided the superficialness of some textbooks. The Reviewer commends particularly its wealth of small but essential detail, and its emphasis on the need for a meticulous technique and a conservative attitude, essential for patient safety. The book may be warmly recommended to those concerned with any phase of transfusion from donor selection to the clinical use of whole blood and plasma.

W. B.

PHYSICAL MEDICINE. The Employment of Physical Agents for Diagnosis and Therapy. By FRANK H. KRUSEN, M.D., F.A.C.P., Associate Professor of Physical Medicine, The Mayo Foundation, University of Minnesota; Head of the Section on Physical Therapy, The Mayo Clinic, etc. Pp. 846; 351 illustrations. Philadelphia: W. B. Saunders Company, 1941. Price, \$10.00.

This is a welcomed edition to the textbooks on this important and growing subject. The author has carried out a definite plan which includes the physics, method of production, physiologic effects, technique, indications and contraindications of each subject. This makes a very effective and complete covering of each subject considered and enables the physician to obtain the desired information without having to digest too much extraneous material. Each subject is also covered by a full reference to literature and the opinion of various authorities on the subject. As the opinions are at times directly opposed, there is a tendency for one to become confused if he ventures too far into the résumé of the literature. For those who want to pursue the subject, it constitutes a very valuable source of information.

Artificial Fever is covered in a very complete and concise manner and presents a modern concept of the entire subject of fever therapy in a very practical way. This is one of the best features of the book. Various types of electrotherapy are very clearly discussed and their indications and

technique properly described. Of particular value are the chapters on Diathermy where the author has assumed a very sensible attitude without dogmatic statements. The use of diathermy in diseases of various parts of the body is discussed but unfortunately the directions as to technique is not definite enough to enable the beginner to employ these methods intelligently. The chapters on Hydrotherapy and Mechanotherapy fill a very valuable place as these are subjects which are all too frequently neglected and information on their use is only to be found in specialized textbooks. Inasmuch as they should be associated with the use of Physical Therapy, it is a very valuable thing to have them so well covered by a textbook of this type.

The seventh chapter of the textbook dealing with the clinical aspect of physical medicine discusses its use in the various specialties and is principally a quotation of the opinion of various authors on the use of Physical Therapy in these various specialties. The chapter is very valuable to one who is well versed in physical therapy but for the beginner there is too much of a tendency to confuse the issue as no definite statements are made as to the author's stand on the various subjects.

In general, the book fills a long-felt need and will be of great value to the present practitioner as well as to the beginner in the use of Physical Therapy.
W. S.

FROM INFANCY THROUGH CHILDHOOD. By LOUIS W. SAUER, M.D., Ph.D., Assistant Professor of Pediatrics, Northwestern University Medical School, Chicago; Physician, Evanston Hospital, Evanston, etc. Pp. 200; 13 illustrations. New York: Harper & Brothers, 1942. Price, \$2.00.

THIS volume, in size and content, can be classified as a pocket manual or guide book to child-bearing and child-rearing. In a simple and condensed manner it covers, in a practical way, the more common problems presented by the prenatal period, a discussion of breast and bottle feeding, and a résumé of vitamin requirements and balanced diets.

The physical and mental health of the infant and growing child are briefly considered, as well as the more common diseases of childhood.

A chapter is devoted to the special problems of the premature infant, and another to the adopted child. In an appendix is included the more frequent accidents that may befall the child, and a list of poisons and antidotes.

The author does not intend that the book be more than a practical guide to be used in conjunction with, not instead of, direct medical supervision. As such, the volume is well composed, and so written as to be readily comprehended by the average mother.
M. C.

DIABETES MELLITUS. By ZOLTON T. WIRTSCHAFTER, M.D. and MORTON KORENBERG, M.D. Pp. 186. Baltimore: The Williams & Wilkins Company, 1942. Price, \$2.50.

THIS book of 13 concise and clearly written chapters, has been written, according to the authors' preface, for the information of those who wish to understand the abnormal processes which underlie diabetes and what may be accomplished in the way of treatment. It is in no sense a textbook from which details of treatment may be obtained. One of the valuable features of the book is a bibliography of over 300 scientific articles which includes the most important literature of recent years on the subject of diabetes. The book is well indexed so that subjects are easily found. The reading is easy, but one might wish that the authors had treated the chapters on vitamins and endocrines more fully. However, the book is a valuable contribution to the literature on diabetes.
R. R.

NEW BOOKS.

The Structure of Protoplasm—A Monograph of the American Society of Plant Physiologists. By WILLIAM SEIFRIZ. Pp. 283; illustrated. Ames: Iowa State College Press, 1942.

Surgery of the Ambulatory Patient. By L. KRAER FERGUSON, A.B., M.D., F.A.C.S., Lieut.-Commander, Medical Corps, U. S. Naval Reserve; Assistant Professor of Surgery, University of Pennsylvania, etc. With A Section on Fractures by LOUIS KAPLAN, A.B., M.D., F.A.C.S., Associate in Surgery, University of Pennsylvania. Pp. 923; 645 illustrations. Philadelphia: J. B. Lippincott Company, 1942. Price, \$10.00.

The Conquest of Bacteria—From Salvarsan to Sulphapyridin. By F. SHERWOOD TAYLOR. Foreword by HENRY E. SIGERIST. Pp. 175. New York: Alliance Book Corporation, 1942. Price, \$2.00.

The Clinical Application of the Rorschach Test. By RUTH BOCHNER, M.A., Psychologist; Formerly Bellevue Psychiatric Hospital; and FLORENCE HALPERN, M.A., Psychologist, Bellevue Psychiatric Hospital. Introduction by KARL M. BOWMAN, M.D., Professor of Psychiatry, University of California Medical School, San Francisco, Calif. Pp. 216; 20 records. New York: Grune & Stratton, 1942.

Pediatric Gynecology. By GOODRICH C. SCHAUFFLER, A.B., M.D., Assistant Clinical Professor of Obstetrics and Gynecology, University of Oregon Medical School, etc. Pp. 384; 66 figures. Chicago: The Year Book Publishers, Inc., 1942. Price, \$5.00.

Neural Mechanisms in Poliomyelitis. By HOWARD A. HOWE, M.D., Associate in Anatomy, The Johns Hopkins University, Baltimore, Md., and DAVID BODIAN, Ph.D., M.D., Assistant Professor of Anatomy, Western Reserve University, Cleveland, Ohio. Pp. 234; 58 illustrations. New York: The Commonwealth Fund, 1942. Price, \$3.50.

L'état Pré-cancéreux-Signification Biologique. By J. M. MONTPELLIER, Professor of Pathological Anatomy, School of Medicine, University of Algiers, North Africa. Pp. 268; numerous illustrations. Algiers: Jules Carbonel, 1941. Price, about \$2.00.

The Schering Clinical Guides. A Three-volume Review of Modern Sex Endocrinology. Vol. 1—Female Follicular Hormone Therapy—58 pages. Vol. 2—Corpus Luteum Hormone Therapy—47 pages. Vol. 3—Male Sex Hormone Therapy—52 pages. Prepared and published by the Schering Medical Research Division, Schering Corporation, Bloomfield, N. J., 1942.

NEW EDITIONS.

The Principles of Neurological Surgery. By LOYAL DAVIS, M.S., M.D., F.A.C.S., Ph.D., D.Sc. (Hon.), Professor of Surgery and Chairman of the Division of Surgery, Northwestern University Medical School, Chicago, Ill. Pp. 503; illustrated, with colored plates. Second Edition. Philadelphia: Lea & Febiger, 1942. Price, \$7.00.

Symptom Diagnosis. Regional and General. By WALLACE MASON YATER, A.B., M.D., M.S. (IN MED.), F.A.C.P., Professor of Medicine and Director of the Department of Medicine, Georgetown University School of Medicine; Physician-in-Chief, Georgetown University Hospital; Physician-in-Chief, Gallinger Municipal Hospital, Washington, D.C. Pp. 900. Fourth Edition. New York: D. Appleton-Century Company, 1942.

PROGRESS OF MEDICAL SCIENCE

THERAPEUTICS.

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,

AND

HARRY GOLD, M.D.

ASSISTANT PROFESSOR OF PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY

WHAT THE U. S. PHARMACOPŒIA XII MEANS TO THE PHYSICIAN.

BELIEVING that every physician owes it to himself and to his patients to keep fully informed in the field of therapeutics, the editors are of the opinion that this department can serve its readers best by discussing the forthcoming Pharmacopœia of the United States, U.S.P. XII. Unfortunately, the majority of physicians seem to know little or nothing about this great compendium which makes it possible for them to treat their patients safely and as skilfully as their therapeutic knowledge permits. The United States Pharmacopœial Convention of 1940 adopted 26 general principles to govern the work of revision the first of which is: "The object of the Pharmacopœia is to provide standards for drugs and medicines of therapeutic usefulness or pharmacutic necessity, sufficiently used in medical practice within the United States or its possessions; to lay down tests for the identity, quality, and purity of these; to insure, so far as practicable, uniformity in physical properties and active constituents. It is recommended that the Committee of Revision be authorized to admit into the Pharmacopœia a carefully selected list of medicinal substances of known origin, but no substance or combination of substances shall be introduced if either the composition or mode of manufacture thereof be kept secret." This defines clearly the purpose of the volume and specifically limits its scope. Congress, by the terms of the Food, Drug and Cosmetic Act establishes each revision as the law of the land with reference to the substances described therein and which thereafter are termed "Official." The U.S.P. thus provides authoritatively a selected list of substances and their preparations which are of definitely established therapeutic value in the light of the best current scientific knowledge. It then seeks to establish all workable means to insure to both physician and patient

that these official agents shall be of uniform purity and standard potency.

The process of revision is a task of far greater magnitude and difficulty than can well be appreciated by anyone who has not participated. It is performed under the direction of the Committee of Revision made up of about 50 recognized experts elected by the Convention from those who are willing and are best qualified to serve. This group represents almost every special field covered by the Pharmacopœia, including Medicine, Pharmacy, Pharmacology, Chemistry, Physiology, Biochemistry and many of the fields allied with each. It is aided by subcommittees, special advisory boards and other groups of authorities on particular topics or in special fields such as the hormones, anti-anemia preparations, etc., even reaching so far as to include problems of packaging of drugs to prevent change or deterioration during storage. As an illustration, considerable research was required to determine the composition, color and thickness of glass to permit the establishment of proper specifications for bottles, ampoules and similar containers. Even the services of statisticians have been utilized in the further perfection of assay methods. In brief, there are few branches of modern scientific knowledge which have not been called upon to participate in the preparation of the forthcoming U.S.P. XII.

The selection of agents on the basis of therapeutic usefulness, or the rejection of others, is entrusted to a group of medical authorities and teachers who compose the Sub-committee on Scope. This committee is empowered to secure help and advice from any available source so that its final selections, while doubtless not perfect, are certainly representative of the best current scientific judgment. The Committee on Scope has tried to evaluate both the agents themselves and such preparations of them as are made available and has endeavored to restrict inclusion of preparations to those proved therapeutically most useful and satisfactory. In so doing the range of preparations or even of similar agents has been made wide enough to meet all medical needs. For example the group of hypnotics extends from those whose actions are rapid to those which act slowly; from those having relatively brief action to those which act for many hours; from those which may be administered by mouth to those which may be used parenterally, etc. The patient's requirements thus can be met if his physician knows both his therapeutics and his Pharmacopœia. The practitioner failing to find in the Pharmacopœia a drug which he has previously prescribed would do well to restrain any feelings of resentment until he has made certain that the official drugs will not serve him and his patient quite as well, or probably even better than his old favorite or one that is not official.

As a result of studied and scientific limitation both of drugs admitted and of the number of preparations of any single drug or therapeutic class of drugs the Pharmacopœia does much to simplify the physician's task of prescribing. Furthermore, complex mixtures are not included. Of course the prescriber is left entirely to his own medical judgment in his use of the drugs. He may prescribe them singly or in any combination which appears to him most suitable. In effecting combinations the physician has access in the text to information which will enable him to avoid incompatibilities of chemical and physical nature. The description of each drug states its important physical properties, its

chemical composition, solubility and any other characteristics which may influence its use in prescriptions.

Pleasant vehicles are described, along with their formulæ. With accurate knowledge of the drug thus at hand an appropriate vehicle may be chosen. But the U.S.P. XII goes even further and offers tablets, capsules and other dosage forms for many drugs. It even sets standards and specifies suitable menstrua for the solution or suspension of drugs which may be administered parenterally and recommends appropriate concentrations of the contained drug. It has been urged that the monographs which make up the major part of the volume, so far as it interests physicians, should include suggestions and recommendations regarding the therapeutic usefulness of each drug, or at least of those of recent introduction. This idea wisely has been rejected as outside the scope of a book of descriptions, standards and tests to insure constancy of therapeutic agents. Therapeutic usefulness of a drug is a matter of pharmacopœial concern only so far as it bears upon the problem of inclusion of a drug in the Pharmacopœia. Beyond that the therapeutic responsibility of the Revision Committee ends.

The Committee of Revision has established and stated average doses for substances intended for therapeutic purposes in conformity with a resolution of the Convention: "to state, where feasible, the average (neither minimum nor maximum) dose for adults, and, where deemed advisable, also for children. The term 'average dose' is to be interpreted as the dose which might reasonably be expected to produce the therapeutic effect for which the substance is most commonly employed." It is further stated expressly that these doses are not binding upon the physician who may exceed them whenever his judgment renders that advisable. Again the Convention has intentionally avoided an important therapeutic problem which is exclusively for the physician to solve for each individual patient. The statement of dose is made solely as a guide to the best accumulated experience and wholly without any implied recommendation. The doses were determined by vote of a large number of recognized authorities, and in some instances advice was obtained from the members of the special board concerned, such as the Anti-anemia Board, or the Hormone Board. The practitioner is thus guided authoritatively yet left free to use his own best judgment.

Potent remedies are made to conform, so far as is advisable, to international standards as established by the International Protocol of Pharmacopœial Experts. Wherever possible potency is based upon chemical methods of assay. There are many substances for which this is not yet possible and for these some biologic method is required. A vast amount of study has been given to the final selection of the particular method so that it shall be the best available at the time of publication. More will be said on this subject later, but the medical profession owes much to the labors of the Sub-committee on Bio-assay which is responsible for choice of method, for its critical analysis and testing and for the detailed directions for its actual performance.

These represent only a few illustrations of what the Pharmacopœia means to the physician if he would but avail himself of its many services to his daily needs. The price of the new revision will presumably be higher than that charged for its predecessor, to which doubtless there will be some objections, however unjustified they may be. The

fact is that the revenue from sales covers only a small fraction of the total cost of revision. Several hundred thousands of dollars have been spent on research alone, most of which has been contributed by manufacturers, institutions of learning, government and other laboratories, etc., both in money and in the form of facilities and the skill and labors of those who have graciously and faithfully devoted themselves to the many and often complex tasks involved. A debt of profound gratitude is due to all who have so generously given of their funds and labors to make the volume as nearly perfect as possible. The price would be utterly prohibitive if it were based upon the actual costs of revision. Physicians can discharge this debt by making full use of the U.S.P. as a reference work of great value to them within daily practice.

We may now turn from the general to the specific and comment upon particular aspects of the Pharmacopœia.

Biologic Standardization. One of the most vital activities of pharmacopœial revision relates to the biologic standardization of drugs. Some of the most useful agents in the realm of therapeutics belong in this group. They are materials which vary in potency from batch to batch and for which there exist no chemical tests of potency. Without security that their strength is uniform, there is chaos in therapeutics.

The problem involves the testing of materials on animals and adjusting the finished product in such a manner that a given amount of different batches will produce the same effect. The group of therapeutic agents in daily use which requires biologic standardization includes the following: digitalis and preparations related to it, ergot, epinephrine, solution of posterior pituitary, parathyroid, insulin, estrogenic and pituitary materials, some of the vitamins, anti-anemia products (liver), serums and antitoxins.

The magnitude of the problem of establishing suitable methods of biologic standardization is not generally appreciated by the practising physician, although he may be fully aware of its importance. Animals that are used for standardization, like humans, vary in their sensitiveness to drugs. Even the average response for a group of animals may differ from the average response for another group tested under somewhat different conditions and by different bio-assayists. Furthermore, not all species of animals behave alike in response to certain drugs. For example, when preparations of digitalis are compared in the frog one often obtains results which are different from the results obtained in a similar comparison using cats. The selection of the most appropriate method is one of the major problems, since for most products numerous methods are described in the scientific literature. An endeavor is made, by comparisons in humans, to select that animal method which gives results most nearly applicable to humans. Sometimes slight variations in the details of the technique will yield different results. The method needs to be described in such detail as to insure similar results in the hands of bio-assayists in different parts of the country. The Pharmacopœia has the effect of law. The method must be so devised and described that different manufacturers of similar products may feel secure that they comply with the standard requirements of the Pharmacopœia since they are liable to prosecution if a product, labeled "U.S.P.," fails on reëxamination to comply strictly with its standard. The Pharmacopœia takes every measure available to insure uniformity of a product. Animal studies have shown that

the most uniform results are obtained if a product of commerce is compared with a standard material and the result expressed in terms of the standard. The Pharmacopœia supplies these standard materials to bio-assayists in the case of drugs for which standard materials exist. The Pharmacopœia has availed itself of the developments in statistical methods of the analysis of data in biologic standardization. Such analyses not only enable the bio-assayist to determine how potent a given material is in relation to the standard product, but to ascertain further the reliability of the standardization, the degree of likelihood that a given result is correct and not accidental. If, in a given case, the index of reliability as established by the statistical device is too low, the Pharmacopœia requires that the assay be repeated or improved. This technique has been applied to some of the biologic standardizations. The use of statistical methods marks a great advance in the safeguards for insuring uniformity in the strength of the medicinal agents of pharmacopœial status.

Insulin. The properties of insulin are such as to necessitate its most accurate and meticulous control. This has been exercised faithfully and efficiently by the Canadian owners of the patent. The recent expiration of the patent would have left the public unprotected against exploitation by careless or unscrupulous manufacturers and importers of the life-saving, yet potentially dangerous therapeutic agent, had this Revision Committee and the Board of Trustees of the U.S.P. not been alert to the situation. Insulin was made official in U.S.P. XI, the current Pharmacopœia, by the issuance of an Interim Supplement to cover the period between the expiration of the patent and the publication of the forthcoming twelfth revision, which will probably become official early in the autumn of 1942. By a special act of Congress the definition, description, strength, methods of assay, tests for purity, packaging and other details for control as given in the monograph contained in the supplement have become the law which will insure to physicians and the laity the future continued supply of a completely trustworthy insulin. Without such action the governmental authorities would have been without legal standards for the protection of the public against really great risks. An act of Congress now requires that each lot of insulin manufactured here or imported shall be checked by the Food and Drug Administration before it is released for distribution.

Digitalis. The twelfth revision of the Pharmacopœia has made extensive changes under the subject of the digitalis materials, in line with scientific developments of recent years. It has extended the scope to include not only basic preparations, but certain dosage forms. It now describes Powdered Digitalis, Tincture of Digitalis, Digitalis Capsules and Digitalis Tablets for oral administration. It also includes several preparations for intravenous and intramuscular administration, namely, the Digitalis Injection which describes in effect the ampoule of the purified mixture of digitalis glycosides. In addition, there is described the Ouabain Injection and Strophanthin Injection, as sterile solutions of these purified glycosides for parenteral use. The Pharmacopœia has therefore established standards for such a wide variety of preparations of digitalis materials as to meet every therapeutic need. The inclusion of capsules and tablets in the Pharmacopœia is a matter of considerable importance. It is one thing to establish a standard for the basic material and another to maintain that standard when the

material is put up into capsules or tablets, since in these inaccuracies may appear and the material may be altered by admixture with excipients and other cohesive materials. The Pharmacopœia describes the details of techniques by which the potent principles may be extracted from capsules and tablets for purposes of assay in order to insure that these dosage forms comply with the standard requirements.

One of the most serious problems in the use of digitalis preparations of commerce is the great multitude of products and the wide variety of potencies among them. The twelfth revision of the Pharmacopœia has established new safeguards to insure uniform potency among all the digitalis materials of Pharmacopœial status. The frog method has been replaced by the cat method as the official method of biologic assay. The two methods have been found to give different results regarding the relative potency of digitalis preparations. Extensive clinical experience and special experiments in humans designed to test which results are more applicable to man showed that the frog method is often misleading, and that the results by the cat method more nearly represent the relative potency of any two preparations in humans. This change was not made lightly. A special committee comprising cardiologists, bio-assayists and pharmacologists was established to study the problem. A detailed description of the new assay method was not only written but tested in a series of collaborative assays involving a large number of laboratories throughout the United States and Canada. After numerous corrections made as the result of these experiences with the method, it was found to give extraordinarily uniform results in the hands of different laboratories. In addition, a statistical device has been introduced by which the Pharmacopœia requires that the assayists not only secure an answer, but also an index of the likelihood that the answer is correct.

The greatest uniformity in the strength of digitalis preparations is assured by assaying these preparations against a standard material, the Digitalis Reference Standard of the Pharmacopœia, and 0.1 gm. ($1\frac{1}{2}$ gr.) of this digitalis power is defined by the Pharmacopœia as 1 U.S.P. Unit. The standard powder is supplied by the Pharmacopœia to those who standardize digitalis. The physician may then expect that if he administers 1 U.S.P. Unit of digitalis power, or of a tincture of digitalis, or of some water-soluble injectable solution, the effects of each in man will be identical, since each will represent the effect of one and the same thing, namely 0.1 gm. ($1\frac{1}{2}$ gr.) of the Digitalis Reference Standard. The amount by weight or measure matters little. In 1 case it might be 2 cc. of a solution, in another case 1 cc. What does matter is that the same amount of potent material is administered, and this can be secured by dosage in terms of U.S.P. Units. For those who have been thinking in terms of cat units, it might be stated that 0.1 gm. ($1\frac{1}{2}$ gr.) of the U.S.P. Digitalis Reference Standard or 1 U.S.P. Unit will represent approximately 1.3 cat units. In the case of the solutions of Ouabain and Strophanthin for parenteral administration, the dose of the drug is expressed in milligrams, without reference to any unit, and both are assayed against the Ouabain Reference Standard of the Pharmacopœia, a pure crystalline material.

There is little doubt that the changes which have been introduced into the forthcoming revision of the Pharmacopœia in relation to the

digitalis materials will greatly simplify their use and assure for their application in man a degree of uniform potency among market preparations such as has not been attained in the past.

Ether. The Pharmacopœia describes two qualities of ether. One is called "Ether," the other is called "Ethyl Oxide" or "Solvent Ether." More rigorous tests for purity are applied in the case of "Ether," since this is the only one to be used for the purpose of anesthesia. The article on anesthetic ether has in the past included a statement to the effect that ether to be used for anesthesia must be preserved only in small, well-closed containers, and is not to be used for this purpose if the original container has been opened longer than 24 hours. This caution was based on the belief that ether deteriorates very quickly when the container is opened, and under those conditions becomes unfit for anesthesia after 24 hours. The result of this requirement has been the purchase of ether by hospitals in very small containers of $\frac{1}{4}$ or $\frac{1}{2}$ pound. What remained unused for anesthesia was subsequently used for cleansing or solvent purposes. This was a very costly practice and one that resulted in great waste of highly purified anesthetic ether.

The forthcoming U.S.P. XII has revised this requirement. It allows ether to be used for anesthesia from containers with a capacity as large as 3 kg. Furthermore, it recognizes the fitness of the ether for anesthesia even after the container has been opened for an indefinite period. It is no longer therefore necessary to discard the costly anesthetic ether 24 hours after the container is opened. There is, however, the safeguard against deterioration in unsuitable containers in the requirement that ether is not to be used for anesthesia if it has been removed from the original container longer than 24 hours.

Scientific studies during the past several years have confirmed the fact that the metal containers in which anesthetic ether is supplied are of very high quality, that ether stored in them retains its purity indefinitely, and that in improperly prepared containers, deterioration is likely to take place fairly rapidly. The more recent studies have also shown that anesthetic ether in the metal containers in which it is supplied retains its purity for weeks and months even if the metal seal is removed and the container stoppered with cork. Experience involving thousands of surgical cases now exists in which it was found that bulk ether removed from cans which had been opened many times and stoppered with cork during a period of months produces a quality of anesthesia that is indistinguishable from that of the ether in a freshly opened can.

The Pharmacopœia has taken cognizance of these developments in its revised standards for anesthetic ether. Several large hospitals in various parts of the United States are now using bulk ether for surgical anesthesia in this way. Anesthetic ether in bulk costs only about one-fifth as much as the same ether in the $\frac{1}{4}$ pound containers, a very considerable saving, since the yearly consumption of anesthetic ether in the United States amounts to about \$1,000,000. This saving is accomplished without the slightest compromise with the efficacy of the anesthesia or the safety of the patient.

(To be continued in the November issue.)

CARY EGGLESTON, M.D.
HARRY GOLD, M.D.

RADIOLOGY.

UNDER THE CHARGE OF

CHARLES G. SUTHERLAND, M.D.

ASSISTANT PROFESSOR OF RADIOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

THE RÔLE OF ROENTGENOLOGIC EXAMINATION IN
DIAGNOSIS.

PERCY BROWN,² in a review article, emphasizes the importance of the discovery of the Roentgen ray for the medical world. The ardent minds that first perceived in this new gift of physical science a latent promise to medicine seized on it eagerly and forthwith to adapt it as far as possible to clinical needs.

Considering nasal sinusitis, Grier⁶ has shown that an antrum filled with polypoid tissue might exhibit the same image on the roentgenogram as one filled with pus. The knowledge that polyps were present in the nose or that pus was draining from the antrum would enable the roentgenologist who interpreted the roentgenologic characters to make the diagnosis. He believes that the diagnosis can be accomplished best in routine practice by correlation of the data from the rhinologic and roentgenologic examinations with full understanding of the limitations of roentgenologic examination. In the field of diagnosis, what this author pointed out as a requisite in this particular field applies generally. Primary roentgenologic examination must always be regarded as part of a coöperative effort, with mutual appreciation of the advantages and disadvantages of each individual method. Wherever such an arrangement has prevailed, devoid of exploitation of the advantages of the individual method by individuals, the most satisfactory results from the standpoint of the patient have been attained.

The basic factor in the advantage of primary examination with the aid of the Roentgen rays is exemplified in a statement of Graham⁵ made in the discussion of the criteria of malignancy. He stated that all organs and tissues have an architectural plan which is looked on as being normal. Any deviation from this plan immediately raises the question of either a benign or malignant neoplastic process. Growth of the epithelial cells of the skin outward to form villus-like processes usually indicates a benign neoplasm; growth into the dermis or subcutaneous fat usually indicates a malignant neoplasm. Similarly in the intestine growth into the lumen of pedunculated masses usually indicates a benign lesion; if into the submucous or muscular coats, usually a malignant. This architectural derangement can be depicted in the roentgenogram in many types of pathologic processes and nearly all the facts that Graham established as indicative of the nature of a lesion can be elicited in Roentgen examination. He recognized the necessity of correlation of the data of the physical and all other examinations with that of the pathologic study in the establishment of the ultimate diagnosis. The significant note of his presentation was that on the basis of accumulated experience certain conclusions were accepted generally.

Another advantage of roentgenologic examination as an aid in diagnosis was pointed out by Rigler⁹ in the report of a roentgenologic sign of pneumoperitoneum, hitherto not reported or at least not clearly defined. A definite outlining of the outer and inner parts of the intestinal wall by the accumulation of gas between the loops of the bowel might depict the first evidence of the presence of pneumoperitoneum in some cases in which such a condition was entirely unsuspected.

In roentgenologic study of acute infections of the respiratory tract of children, Bouslog¹ divided the respiratory tract at the lower end of the pharynx into upper and lower portions that have anatomic and physiologic distinctions. While the mastoid processes do not aid in the preparation of the air for the lungs, they are directly connected with this upper part through the Eustachian tube; they were therefore included as a part of this tract. The pharynx, he believed, had a specialized and distinct function which was chiefly mechanical, involving the sphincter action of the glottis in governing the quantity and pressure of the intake of air. Physiologically, each division of the respiratory tract played a more or less independent rôle and had a somewhat dissimilar function to perform, but all functioned in harmony. Their chief use was to facilitate the passage of the air to the alveoli. The air was filtered and heated in the upper part of the respiratory tract to prepare it for oxygenation of the blood and distribution to the tissues concerned in this procedure. He pointed out that Mullin and Ryder had demonstrated the connection of the lymph drainage of the upper air passages and accessory sinuses with the lungs. He credited Pfahler with having demonstrated roentgenologically the lymph drainage from the maxillary sinuses to the thoracic duct by injection of lipiodol into the maxillary sinuses. Bouslog was of the opinion that a study of the mastoids, sinuses and thorax of all patients having acute infections of the respiratory tract would not only elicit a better understanding of the underlying pathologic processes, but also would give a better interpretation of the presenting signs and symptoms and thus permit intelligent treatment of such patients. With the belief that the mastoids and sinuses were involved more frequently than was generally realized, and the knowledge that a great majority of infants afflicted with severe gastro-intestinal disturbances as the outstanding symptom also have accompanying foci of infection in the mastoids, he studied a series of cases of acute infection of one of the divisions of the respiratory tract.

The conclusions from this study were that frequently acute infections in some division of the respiratory tract were more serious than the infection in another division which had been regarded as the factor producing the symptoms. Early, accurate diagnosis of such infections and adequate treatment, Bouslog thought, might prevent the occurrence of some of the chronic diseases of adult life.

In an article on intrathoracic neurogenic tumors, Kornblum and Bradshaw⁷ brought out once more the value of Roentgen ray examination of the thorax, and that Roentgen examination afforded the best means of detecting intrathoracic neoplasms. They stated that the signs and symptoms of these lesions were often few and slight and frequently were lacking entirely. They remarked that it was astounding how large a tumor within the thorax might become before giving rise to

symptoms; such tumors have been accidentally discovered in routine examinations. They pointed out certain clinical and roentgenologic features which served to distinguish one tumor from another so that a critical correlation of roentgenograms with clinical signs often serve to establish a correct diagnosis.

Kornblum and Bradshaw asserted that neurogenic tumors of the thorax did not appear to have any predilection for sex or age. The clinical manifestations were not striking in most instances. The onset of symptoms was usually insidious. The rapidity of the course depended largely on whether the tumor was benign or malignant. The symptoms, largely those of pressure, were dependent on the structures on which pressure was exerted. The majority of neurogenic tumors occurred in the posterior part of the thorax, well away from any of the vital structures contained in the mediastinum. Here they might attain a considerable size before giving rise to manifestations of pressure.

Among the more constant and prominent symptoms were pain in the thorax and cough, either perhaps predominating. Because of their size, many of these tumors caused interference with normal pulmonary physiologic procedures by pressure. Interference with drainage of the lungs and the occurrence of atelectasis invited infection. Atelectasis was more prone to occur with tumors arising in the mediastinum which permitted the larger bronchi to be compressed. This was likewise true of pleural effusion, which was occasionally encountered. Paralysis of the phrenic nerve was also a manifestation of a mediastinal origin of the tumor. It was possible for a tumor to arise in the thorax and project into the vertebral canal.

These authors recommended that the routine Roentgen investigation for intrathoracic neoplasms should include a careful roentgenoscopic observation and an adequate roentgenographic study.

Considering the differential diagnosis, Kornblum and Bradshaw stated that lymphoblastoma, Hodgkin's disease and lymphosarcoma usually were confined to the mediastinum and produced in it a nodular enlargement. Lymphatic enlargements elsewhere in the body, from which specimens could be taken for biopsy, served as an aid in establishing the diagnosis. The rather prompt and striking response of lymphoblastoma to irradiation offered a valuable aid to diagnosis, in that the neurogenic tumors were highly radioresistant. Their experience had been that when lymphatic leukemia produced a pathologic change in the mediastinum, it was practically never an isolated process. A study of the morphology of the blood cells would reveal the true nature of the disease when lymphatic leukemia was present. Aneurysm of the thoracic aorta could be recognized most frequently by establishing its origin from the aorta in roentgenoscopic observation. Thymomas, in their experience, were confined to the mediastinum and their outlines in roentgenograms were usually irregular in contrast to the sharply demarcated shadow of the dermoid cyst. The thymoma, dermoid cyst and substernal or intrathoracic goiter occurred anteriorly in contradistinction to the posterior location of the neurogenic tumor. The goiter frequently compressed or caused deviation of the trachea and could be observed on roentgenoscopic study to alter its position with deglutition. Single, large, isolated malignant metastatic nodules, and intrathoracic fibromas or lipomas might be difficult to distinguish

from neurogenic tumors. The making of the differential diagnosis could be important, because the only treatment that was of any avail in neurogenic tumors was surgical removal.

The frequency with which the respiratory tract and such other sites as the gastro-intestinal tract, the skeletal system and the genito-urinary tract were affected by lymphoid diseases is not well recognized. This statement was made by Vieta and Craver¹⁰ after a study of 1911 cases. Of this group of 1911 cases, they found that 794 were acceptable for roentgenographic study and 160 for an analysis of findings obtained at necropsy. Necropsy revealed that the incidence of intrathoracic lesions was much higher than was indicated by the roentgenographic studies that were made. These authors were of the opinion that more frequent Roentgen examination of the thorax was indicated by their study. The roentgenographic features lent themselves to analysis in subgroups as follows: 1, mediastinal tumor; 2, infiltration into the parenchyma of the lungs; 3, isolated nodules in the parenchyma; and 4, discrete nodules at the roots of the lungs. They also added two further subgroups, pleural thickening and pleural effusion. In their series they did not notice any particular frequency of enlargement of the right paratracheal nodes in Hodgkin's disease. Infiltrations into the parenchyma of the lungs, extending out from the hilus, considered diagnostic by some, occurred also in their experience in sarcoid of Boeck, tuberculosis of the tracheobronchial lymph nodes and metastatic carcinoma. They quoted Lenk as having observed that the clinical picture of tuberculosis in conjunction with the Roentgen characters of malignant tumor favored a diagnosis of Hodgkin's disease. Isolated nodules in the lung, almost invariably accompanied by one or more of the other types of intrathoracic manifestations of lymphoid disease, they considered as true metastasis after consideration of the fact that the Hodgkin's process must be disseminated through the body, either through the blood or lymph channels, to reach the bones and the structures of the nervous system, both of which are grossly devoid of lymphoid elements.

In a study of 335 cases, Vieta and Craver found mediastinal tumors in 47.4 %, infiltration into the parenchyma of the lung in 38.5 %, isolated nodules in 5.3 %, discrete nodules at the roots of the lungs in 23.8 %, pleural thickening in 7.4 % and pleural effusion in 15.8 %.

From the roentgenographic study these authors were impressed by the frequency with which intrathoracic structures were involved in Hodgkin's disease. The protean features of the lesions, however, led to the conclusion that there were no specific roentgenologic features that would allow the roentgenologist to make more than a presumptive diagnosis of lymphoid disease. In their experience, the lungs were probably more often invaded than any other structure with the exception of the lymph nodes. In 335 cases observed clinically and pathologically in their series, they did not find a single case in which they could state definitely that the parenchyma of the lungs was involved primarily and that the other manifestations were secondary. In about 7 % of their cases the first Roentgen examination of the thorax revealed involvement of the mediastinum, hilus or parenchyma of the lungs. There were no cases of primary involvement of the pleura by Hodgkin's disease in their series. In 88 % of the 51 cases in their series in which

necropsy was performed, they found some form of lesion within the thorax caused by Hodgkin's disease.

In malignant tumors of the lymphatic system (reticulum cell sarcoma, malignant lymphocytoma and giant follicular lymphadenopathy) the roentgenographic features were not unlike those of Hodgkin's disease. Displacement of intrathoracic structures, even when the mediastinal or hilar masses were of large size, was rarely noted in lymphosarcoma. Pleural effusion occurred in 16.6% of the cases observed; pleural thickening in 9.6%. Pulmonary involvement or pleural manifestations usually occurred rather late in the course of lymphosarcoma, but despite this, in many cases striking improvement in the patient's general condition followed irradiation of the affected regions. They were of the opinion that, when parenchymal involvement was noted, Roentgen therapy should be used to the full limit. When lymphosarcoma had invaded the intrathoracic structures, the involvement was widespread with the formation of large masses of neoplastic tissue. Their material obtained at necropsy indicated that in 30% of the cases infiltration of the parietal pleura was extensive.

In their roentgenographic study of lymphatic leukemia Vieta and Craver were impressed by the frequency of the parenchymal infiltrations in the lung. Involvement of the mediastinal and hilar nodes occurred most frequently, but at necropsy these nodes were of such dimensions that they would not have been demonstrable roentgenographically. Isolated nodules of leukemic tissue within the parenchyma in lymphatic leukemia were rare phenomena in their experience. In their roentgenographic studies, Vieta and Craver did not find an instance of a mediastinal tumor in a case of myelogenous leukemia.

Dusts as an industrial hazard have had much to do with the ever-widening interest of the directors of industrial corporations in routine *Roentgen ray examination of the thorax as a requisite in preemployment investigations and in connection with arrangements for the maintenance of the health and efficiency of employees.* The commanding position of the roentgenogram in establishing a criterion for the awarding of compensation was exemplified by Clement³ in a study of rock drillers in underground mines and of the conditions under which these miners worked. Follow-up investigations had included consultation with personal physicians of the miners and their families. Persons who had certain types of thoracic roentgenograms did not become disabled but were content in their employment and were able to do a full day's work. Thoracic shadows in such cases, the author pointed out, were not significant of damage that would entitle the person to compensation for disability. Because of the number of times that such illustrations had been used to support the idea of rock dust as an industrial hazard, he was of the opinion that insufficient correlation of data had resulted in false concepts of the significance of the roentgenographic shadows.

Doughty⁴ stated that roentgenologic studies of the lungs afford the most accurate means of diagnosis of silicosis and that serial roentgenograms allow watching the changes as they occur. Although he acknowledged that physicians of large experience in all phases of silicosis, if given the number of years a worker has been employed, an accurate dust count of the air that the individual has breathed and the size of the particles of silicon dioxide in that dust, or if permitted to see a

group of employees walking up a moderate grade to work, could describe accurately the pathologic changes present in the thorax, he still maintained that most competent roentgenologists could achieve a much better average in the diagnosis of silicosis. Their success would necessitate adherence to the usual procedure recognized by the roentgenologist, namely 1, primary roentgenographic examination of the thorax and, 2, correlation of the roentgenologic data with that of, *a*, an accurate history of the subject's employment during his working life, *b*, an accurate dust count made at the breathing level of the patient, *c*, the percentage of silicic acid in the atmosphere breathed and the size of the particles present and, *d*, the findings in the taking of the medical history and the making of the physical examination. Although he acknowledged that a positive diagnosis of silicosis should not be made on the roentgenographic evidence alone, Doughty was of the opinion that an accurate diagnosis of silicosis was not possible without Roentgen examination of the thorax. This author quoted Burge, as follows: "Only the physician who has examined the subject, has obtained an occupational history of an adequate exposure to silica dust, and had before him a suitable roentgenogram of the chest, should make a diagnosis of silicosis. The roentgenologist not in possession of these facts can merely state whether the shadows which he sees in the roentgenogram are consistent with his diagnosis." He emphasized that demonstration of discrete nodules was the one essential in establishing the diagnosis of silicosis. Coalescent nodulation occurred when the nodules became numerous in a fairly small area and the fibrous tissue between them became more evident. He stated that coalescent areas were most commonly seen in the upper central portions of the pulmonary fields, and were almost always bilateral and symmetrically placed. Conglomerate masses usually were due to the merging of a number of these coalescent areas, with the addition of fibrous tissue, into a dense area of larger size. They, too, were usually in the central and upper portions of the pulmonary fields, although they sometimes occupied the greater part of the upper two-thirds of one or both sides. While these infiltrated areas were usually regular, his experience was that at times they might be irregular.

With this concise description of the pathognomonic roentgenographic features of silicosis, Doughty contended that in the follow-up work among employees of dusty industries, serial roentgenograms made every 6 months or every year were more valuable than the data of any other examination. They made an invaluable record for comparison. If in any later roentgenogram the number of silicotic nodules had lessened, then silicosis as a factor in the symptoms could be eliminated. Once established, these nodules never disappeared although they might be obscured as a result of active infection or massive formation of fibrotic tissue.

Complications might alter the roentgenographic image. Emphysema, seen commonly in the older and more advanced cases, began usually in the costophrenic angles and progressed along the diaphragm until it sometimes had occupied the lower fourth or third of the thoracic cage. It was almost always bilateral and symmetrical, in extreme cases with perhaps more lobules on one side than the other. Smaller amounts of emphysema were at times seen in the pulmonary fields surrounding

coalescent or conglomerate areas in the upper and middle sections. Fibrous bands were common in the advanced cases, extending from the dense masses in the upper portions of the lungs through the emphysematous region, causing tenting or peaking of the diaphragm where they were adherent. For some unexplained reason, Doughty found pulmonary tuberculosis to be more common and the mortality rate from it higher in the silicotic than it was in the general population. It was, in his experience, the most common cause of death among patients who had silicosis.

With the advent of industrial compensation in many states, a large number of the older employees in industries where they were exposed to certain forms of dust applied for compensation because of permanent total disability. This author, after a number of years spent in contact with these workers, in which his respect for their stamina and integrity was greatly increased, conceded the justice of their claims. Many of these older employees continued to work long past the time when they should have stopped. Many had advanced silicosis, usually complicated by pulmonary tuberculosis, either active or, more commonly, of the chronic fibroid type. Others showed evidences of the massive conglomerate type of silicosis with associated emphysema, at times complicated by cor pulmonale. Many, however, showed only evidences of simple, uncomplicated silicosis which in itself was not disabling. They were the victims of advancing age, and at the end of many years of hard physical labor they showed the effects of its toll on the human body. The problem of the physician was to determine whether or not silicosis played a part in their disability. The physician fortunate enough to have a series of roentgenograms of the individual concerned extending over a period of 8 or 10 years would find them of great value in the correct analysis of the individual case.

In differential diagnosis of early or moderately advanced cases, many conditions had to be considered such as anthracosis, siderosis, miliary tuberculosis, small metastatic, neoplasms especially of hypernephroma, many of the yeast fungi deposits, sarcoid of Boeck and sprue. In the more advanced cases, pulmonary tuberculosis, cancer, emphysema, bronchiectasis, atelectasis and the pulmonary changes of advancing age had to be considered. With advancing age there was more fibrous tissue in the lungs and the lymph vessels themselves were normally more evident. The roentgenographic image of chronic cardiac disease with the usual accompanying arteriosclerosis and pulmonary changes accompanying compensation might simulate that of silicosis.

Lemon⁸ has stated that all particulate matter in the parenchyma of the lung is disposed of in essentially the same manner and that many particles, both organic and inorganic, were segregated into nodules. Of the inorganic substances, silica (SiO_2) was the most important because it constituted the greatest hazard in the dusty trades; of organic substances, the *Mycobacterium tuberculosis* was the most important because of the important disease it causes. Except for this organism, its reproductive powers, virulence and the allergic reactions it engenders, the response of the reticulo-endothelial system to its presence is substantially the same as the reaction to silicon dioxide. Experimental investigation had proved that silicon dioxide was the specific cause of the disease silicosis. He and his collaborators had found that graphite,

sericite, asbestos, granite and other substances containing silicon dioxide in small concentrations did not, under experimental conditions, produce specific nodular fibrosis, but rather a generalized fibrosis as seen in many conditions classified under the general term "pneumoconiosis." This author⁸ stated that for many years observers had believed that diluents such as coal dust diminished the liability of exposed miners to clinically active tuberculosis. The same idea was applied to silicosis, and for years it was accepted as fact that coal dust acted as an inhibitor to the action of silica. He quoted clinical studies and experimental findings of many observers which seem to substantiate with some degree of certainty the concept that diluent dusts prevent, delay or modify the action of siliceous dust.

Investigation of the size of the particles showed that all observers were in agreement as to the size of the particles of silica that caused damage by becoming arrested within the lungs; these particles must not be too large for phagocytosis by the mononuclear phagocytic cells. The extreme limit in size proved to be 10 μ , and in well-ground quartz and in the dust of mines and dusty trades these large particles were relatively few. To be most effective and most dangerous, the particles measured from 1 to 3 μ . It was possible that these extremely small particles passed in and out of the lung with the air inspired or expired. Those that became arrested were probably very damaging because the degree of damage was, within certain limits, inversely proportional to the size of the particle.

In a study of the specific cell defending the lung against damage, it was determined that silicosis as a disease did not occur because silica was breathed into the lungs, but rather because sufficient dangerous particles were retained within the lung. The disease represented a defect of the defense mechanism resulting in the arrest of the phagocytes after phagocytosis had taken place, and formation of the specific fibrous nodule represented the effort of the organism to segregate, localize and encapsulate the noxious substance so that the least possible degree of harm might result to embarrass respiratory function. Phagocytosis took place largely in the alveoli, not in the larger air passages, and it was from the alveoli that the process of elimination began. The laden phagocytes floated in the serum that escaped from the capillaries, or they migrated along the walls of the alveoli by ameboid movement. In experimental investigation, within a few hours, they were seen to crowd about the terminus of the alveolar duct, which was their first intrapulmonary point of arrest.

Two paths of exit were available for these laden cells: First, they might enter the bronchiole lumen, where changes in pressure and size of the air ducts hurried them along toward the bronchi. Ciliary movements, entanglement in mucus, and muscular action formed the laden cells into a bolus which was readily expelled by coughing. The particles that found exit obviously did not become arrested and did not produce lesions. The second route of removal was by way of the lymph vessels. The lymphatic system is composed of two parts: one superficial and passing toward the pleura, and one deep, following the bronchi and blood-vessels toward the hilus. Lemon and his collaborators proved that arrest occurred and lesions always developed along these systems. They found that laden cells constantly arrived at the

terminus of the alveolar duct and that the stimulation of connective tissue elements constantly augmented their numbers. Cells containing mitotic figures gave evidence that silica promoted hyperplasia in the tissue cell system. Many of these cells became arrested and formed aggregations that created the first cellular lesions, which were ultimately transformed into fibrous pseudotubercles. Thus anywhere along the interlobar fissures, aggregations might be formed in the course of the *pulmonary vein*. *The pleural lymph vessels carried ingested particles* to the bronchopulmonary and tracheobronchial nodes at the hilus, where arrest and concentration of cells created cellular nodules. In experimental silicosis, the laden phagocytes were not readily destroyed; they ultimately became replaced by white fibers and so created in these several situations true silicotic pseudotubercles.

Through the elimination process, Lemon found that the stimulation of the tissue cells continued and early fibrosis occurred along the routes taken by the lymph vessels. Like the primary lesions of pulmonary tuberculosis, all silicotic lesions, regardless of their duration, were subject to changes that operated both within and from the outside of the nodule. When the first concentration of cells formed a microscopic nodule, pressure changes within the lung packed the cells so closely together that they assumed a spherical shape. The cells in the core of the nodule began to undergo degenerative changes. Accumulations of fat occurred in all stages and increased with the size of the nodule. The amount of degenerative change seemed to depend also on the number of particles that were ingested, just as the degree of degenerative changes in the tubercle depends on the number of virulent organisms of tuberculosis within the phagocytes. Both particles of silica and tubercle bacilli are protoplasmic poisons and under experimental conditions both caused fatty degeneration. Later, it was found, the core of the nodule became hyaline or, as in the tubercle, calcium settled there and calcific lesions formed.

The polarizing microscope showed that the particles were most numerous in the core of the nodule and that they became progressively fewer toward the periphery. Nodules of different ages frequently were found in the same section and constituted evidence of the constant changes that tended to destroy them, whether they were of short duration and still cellular, or of long duration and seemingly obliterated by concentric fibrous envelopes or calcification of the core. Observations supported the belief that the action of silica was continuous and that there was no time limit to the duration of the disease, silicosis, in which silica was the specific etiologic agent.

Under prolonged and continuous stimulation, even in the absence of superimposed infection, fibrous changes proceeded. The silica stimulated production of macrophages and fibroblasts. Microscopically discrete pseudotubercles created large conglomerate nodules, and all the perinodular pulmonary tissues were involved in fibrotic changes; the alveolar walls were thickened, the alveoli were compressed, and the bronchioles were deformed into slitlike fissures which were recognizable only because their mucosa and muscular layers had been preserved. These structures were separated by heavy layers of dense fibrous tissue.

When infection supervened, the resultant changes were observed to be similar to those seen in tuberculosilicosis among human beings or

even in simple fibrocascous tuberculosis. The pseudotubercles were no longer discrete but were surrounded by granulation tissue. The parenchymal structures were no longer affected by inflammatory changes, but the finer structures were thickened and deformed and evidence of bronchitis and pneumonia was encountered commonly. As in tuberculosis, ulceration and necrosis progressed and erosion of the vessels and bronchioles occurred. There was also the same tendency toward the formation of thrombi in blood-vessels and lymphatic vessels that was characteristic of tuberculosis produced experimentally by a similar intratracheal technique.

Experimentally produced silicosis, therefore, like silicosis found among human beings, resulted from the interaction of particulate silica and the tissue cell system of the lungs. The nature and the degree of the defense reactions depended on the size, the number and the mass of the particles of silica. The exact cause of the reaction was unknown, but it probably was brought about by the electrochemical effects induced by contact of the particle and the cytoplasm of phagocytic cells. The reaction probably proceeded because the laden cells were not killed but were preserved, and might be concentrated into aggregations of cells situated along the course of the lymphatic system of the lungs. Arrest occurred as a result of phagocytosis and failure on the part of the eliminating mechanism of the lung.

The pathognomonic criterion of experimentally produced silicosis was the discrete pseudotubercle which was pearly-white in color, glandular, and palpable on cut section.

The morbid changes in lungs of experimental animals were controlled by encapsulation, calcification and obliteration by collagenous and reticular fibers. Superimposed infection increased fibrosis in the perinodular parenchyma caused ulceration and necrosis of bronchi and blood-vessels, and brought about the death of the animal by bronchitis, bronhopneumonia and empyema. Simple, uninfected silicosis affected the function of the lungs in proportion to the amount of fibrous tissue that developed, the consequent reduction of vital capacity and the secondary loss of cardiac compensation.

The outstanding feature of this series of presentations is a demonstration of the fact that in roentgenologic investigation opinions are based on the study of graphic evidence. The most rapid and at the same time most accurate means of determining the diagnosis and establishing the prognosis is roentgenologic examination at the time of the primary examination in all types of cases in which this procedure can be made applicable. Correlation of the data on the roentgenologic examination with the results of both clinical and experimental investigations seems to indicate this.

CHARLES G. SUTHERLAND, M.D.

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PHYSIOLOGY.

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF FEBRUARY 17, 1942

A Technique for Demonstrating an Antidiuretic Action of Minute Amounts of Pitressin. WILLIAM A. JEFFERS and MARY M. LIVEZEY (Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania). Single rats rendered diuretic by water, and alcohol in sedative dosage, constitute a satisfactory biologic test for the antidiuretic action of pitressin. It is 10 times more sensitive than Walker's test (Walker, A. M.: *Am. J. Physiol.*, 127, 519, 1939), in which he used the diuretic rabbit; however, the required dose per kilogram of test animal is essentially the same. As an assay technique, using the same number of injections, ours is at least as reliable as the multiple rat test of Burn (Burn, J. H.: *Quart. J. Pharm. and Pharmacol.*, 4, 517, 1931) and as other available tests for antidiuretic substances.

The Activity of the Descending Duodenum in Man During Nausea Produced by Caloric Stimulation of the Semicircular Canals. FRANZ J. INGELFINGER and ROBERT E. MOSS (Evans Memorial, Massachusetts Memorial Hospital, and Department of Medicine, Boston University School of Medicine, Boston, Mass.). A tandem two-balloon system can be "anchored" in the descending duodenum if the balloons are inflated simultaneously when one balloon lies distal, the other proximal to the mid-point of the descending duodenum. A continuous record of duodenal activity can then be taken.

The duodenal activity was recorded in 20 human subjects before, during and after caloric stimulation of the semicircular canals. This procedure produced varying degrees of nausea 13 times in 11 subjects. With the onset of nausea, the descending duodenum underwent a generalized contraction in 8 instances, the degree of the contraction being roughly proportional to the intensity of the nausea produced. In 3 subjects, who experienced a mild "uncasiness," the duodenum appeared to relax. In 2 subjects, vomiting movements obscured the record of duodenal activity.

In 9 subjects who had no nausea after labyrinthine stimulation duodenal activity remained unchanged. When morphine sulfate was given subcutaneously to 5 of these subjects, nausea occurred in each instance and was accompanied by a generalized duodenal contraction. This contraction, and the similar one observed during the nausea which followed labyrinthine excitation, involved both parts of the descending duodenum simultaneously. No reverse peristalsis was noted. Nevertheless, the contracting duodenum expelled both balloons into the stomach 6 times after caloric stimulation and 3 times after morphine.

It appears that nausea, whether produced by labyrinthine stimulation or by the administration of morphine, frequently is accompanied by a generalized contraction of the descending duodenum which tends to expel the duodenal contents into the stomach.

The Mechanism of the Secretion of Sulfanilamide by the Gastric Mucosa. HORACE W. DAVENPORT (Department of Physiology, University of Pennsylvania). When sulfanilamide is present in the plasma it is secreted into the gastric juice. The concentration ratio which is the concentration in the gastric juice divided by the concentration in the plasma has an average value of 2.6, and it varies inversely with the rate of secretion and directly with the plasma concentration. The fact that the concentration in the gastric juice is higher than that in the plasma appears to indicate that thermodynamic work is done on the drug in effecting the secretion. However, a determination of the activity coefficients of the drug in plasma and in gastric juice shows that the ratio of the activity coefficients is 1 to 2.6. Therefore the different concentrations of the drug in the two solutions are actually at or approaching equilibrium. On the basis of the assumption that the drug diffuses through the mucosa at a rate proportional to the difference in activities an equation has been derived which completely explains the gastric secretion of sulfanilamide.

Influence of Anesthetics on the Balance Between Chemoreceptor and Central Control of Respiration. R. D. DRIPPS, JR., and P. R. DUMKE (Department of Pharmacology, University of Pennsylvania). In decerebrate dogs and cats data were obtained, first, on the response of the respiratory center to inhalation of CO_2 , and, second, on the response of the carotid and aortic body chemoreceptors to threshold doses of cyanide injected intravascularly. Original purpose was to determine whether chemoreceptor reflexes are exaggerated in dogs by chloralose; this was found to be the case since the response of the center was regularly diminished and the response of the chemoreceptors regularly elicited by smaller doses after chloralose. Ether, barbital, nembutal, and morphine were also tested in dogs, all these and chloralose, pentothal, and cyclopropane in cats. All drugs depressed the response of the center to CO_2 in both species; this was the only result common to all drugs in both animals. Barbital, like chloralose, exaggerated chemoreceptor activity in dogs, and barbital, morphine, and nembutal did this in cats; morphine in dogs had no consistent effect; nembutal and ether in dogs, and pentothal, cyclopropane, chloralose and ether in cats, diminished chemoreceptor activity. The influence of the narcotic must therefore be considered in the interpretation of experimental results in this field. A partial explanation of the exaggeration of chemoreceptor reflexes mentioned above is the presence of anoxemia resulting from depression of respiration, which occurred with every drug except ether. High O_2 content in the inspired air was found to raise the chemoreceptor threshold to cyanide while low O_2 content had the opposite effect. Summation of anoxic and cyanide stimulation of the chemoreceptors may therefore explain some of these results but it cannot account for the variations among the different depressant agents. Ether, the only drug that did not depress respiratory minute volume, was also the only one that depressed both of the responses in both species; ether must therefore stimulate respiration by other mechanisms among which reflexes aroused by pulmonary irritation deserve prominent consideration.

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Studies With the Electron Microscope. THOMAS F. ANDERSON* (RCA Laboratories, Camden, N. J.) Some of the recent studies with the electron microscope include:

1. The Structure of Elementary Bodies of Vaccinia (with J. E. SMADEL and R. H. GREEN). Vaccinia elementary bodies are roughly rectangular in shape (0.2 by 0.3μ) and contain an internal structure within some sort of a limiting membrane.

2. The Structure and Characterization of Bacteriophages (with S. E. LURIA). A number of strains of anticoli phage were studied and their reactions with *E. coli* followed. "Sperm-shaped" bodies were present in all preparations but the size and internal structure of the "head" as well as the length and thickness of the "tail" were found to be characteristic of the strain of phage. The sizes of these particles correspond roughly to sizes determined by indirect methods. The phage particles seemed capable of adhering to *E. coli* either at the head or with the tail and as lysis progressed the bacteria appeared to be damaged and eventually, of course, to disintegrate.

3. Tissue and Nerve Fibers of the Cat (with G. H. SCOTT). It was found that a cat's nerve, freeze-dried and fixed, could be easily teased apart and mounted for study with the electron microscope, revealing single nerve fibers and connective tissue fibers. Details of the work will be reported elsewhere.

The Bacterial Cell as Shown by the Electron Microscope.—STUART MUDD, T. F. ANDERSON, H. E. MORTON, and K. POLEVITZKY (Departments of Bacteriology, Schools of Medicine and Dentistry, University of Pennsylvania, and RCA Manufacturing Company). Electron microscopic study of a wide variety of bacteria has shown that the bacterium is a cell, with a cell wall distinctly differentiated from inner fluid or potentially fluid protoplasm. Within the inner protoplasm structural differentiation in the form of discrete spheroidal or discoidal granules, or of less definitely circumscribed areas of relatively high density, may often be seen in the electron micrographs. Spores and flagella when present are clearly seen.

The inner protoplasm may be darkened selectively and often shrunk away from the cell wall by exposing the bacterium to solutions of heavy metal salts [e. g., AgNO_3 , $\text{Ni}(\text{NO}_3)_2$]. Exposure to $\text{Pb}(\text{Ac})_2$ has sometimes injured the cell with resultant swelling and escape of protoplasm. These observations point to a possible technology of differential "staining" for electron microscopy, as well as a technique for making visible the effects of germicidal agents on the individual cell.

The specific deposition of antibody on bacterial cells and flagella may be detected through an increase in darkness, thickness and "fuzzi-

* RCA Fellow of the National Research Council.

ness" of the cell wall or flagella, respectively. Deposition of antibody can be seen to be a function of antibody concentration and of time of contact of antigen and antibody.

The Study of Viruses and Proteins With the Electron Microscope.

LESLIE A. CHAMBERS (Eldridge Reeves Johnson Foundation for Medical Physics and Department of Pediatrics, University of Pennsylvania). A series of pictures made with the electron microscope in the Johnson Foundation were used to illustrate the kinds of information relating to proteins and viruses which may be obtained through use of the instrument. Data on size, shape, and interaction of large molecules may be taken directly from the electronmicrographs, when the limitations of adequate contrast and resolution (30 \AA) permit. Some difficulties in the interpretation of density differences in the electron-shadowgraphs were considered.

Exploratory examination of infected chick allantoic fluids indicates that viruses can be identified in such media exactly as bacteria can be identified in smears by ordinary microscopy. Electronmicrographs of the viruses of influenza, equine encephalomyelitis, and herpes simplex were shown, as well as virus-like bodies present in nasal secretions during severe colds.

Carotid and Aortic Body Reflexes in Unanesthetized Dogs. J. G. WATT, P. R. DUMKE, and J. H. COMROE, JR. (Laboratory of Pharmacology, University of Pennsylvania). Experiments were performed on 7 trained dogs to determine: (a) if the carotid and aortic chemoreceptors are tonically active in the unanesthetized dog breathing room air; (b) if the respiratory center of the unanesthetized dog, deprived of carotid and aortic body reflexes, is stimulated by oxygen-lack. Unanesthetized dogs were used since the recent work of Dumke and Dripps (see p. 777 above) indicates that the results of experiments in this field may be dominated by the anesthetic.

Results. (a) Some chemoreceptors are continuously activated by the degree of oxygen unsaturation normally present in the arterial blood of the unanesthetized dog breathing room air, because inhalation of 100% oxygen regularly led to an immediate decrease in pulmonary ventilation. Respiration returned to normal in 1 to 6 minutes despite continued inhalation of 100% O_2 , but during the sixth minute the arterial pCO_2 remained elevated (average increase 3.8 mm. Hg) in 5 out of 6 dogs. After chemoreceptor denervation inhalation of oxygen no longer decreased respiration, but either increased it or had no effect.

(b) Low oxygen mixtures which regularly increased breathing in the normal dog failed to do so after chemoreceptor denervation. A progressive depression of respiration on low O_2 , followed by hyperpnea on changing back to room air was seen in most cases. The absence of stimulation in these unanesthetized denervated animals cannot be attributed to a failure of arterial pO_2 to fall, for with the same 14% O_2 mixture the average pO_2 in the denervated dog was 33 mm. Hg compared to 48 mm. in the intact animal. The primary effect of anoxemia upon the respiratory center of the dog is therefore depression.

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ORIGINAL ARTICLES.

MYOCARDITIS IN POLIOMYELITIS.*

BY OTTO SAPHIR, M.D.,

AND

SIMON A. WILE, M.D.,

CHICAGO, ILL.

(From the Department of Pathology of Michael Reese Hospital and the Sarah Morris Hospital for Children.)

DURING the past few years there have come under our observation several patients with poliomyelitis. Some of these patients succumbed during the acute stage of the disease, while others died rather suddenly several months after the acute process had subsided. It is interesting to note that at autopsy the hearts of some of these patients showed myocardial lesions which must be classed as true myocarditis. Because of these findings and because a search of the literature reveals no pertinent data, hearts of patients dying from poliomyelitis were examined carefully for possible inflammatory changes.

Though no references were found regarding the occurrence of myocarditis in poliomyelitis, there are a few cases on record of myocarditis occurring in other virus diseases. Degen² stated that among 91 hearts of patients who died during the acute stage of measles, 4 showed evidence of myocarditis. This was essentially an infiltration of lymphocytes, frequently but not predominantly perivascular in distribution. Manca⁸ reported an instance of mumps in which the myocardium was the seat of an infiltration of neutrophils, lymphocytes, plasma cells and young fibroblasts. There were also large cells with much cytoplasm and round nuclei whose chromatin formed a coarse "reticulum." Brick,¹ reporting the results of autopsies in 14 cases of whooping cough, found in

* Aided by a grant from the A. B. Kuppenheimer Fund.

one heart a few neutrophils and small accumulations of round cells, and in another, occasional neutrophils throughout the myocardium. Kirch,⁶ in quoting Aschoff, mentioned inflammatory changes in the myocardium of patients dying from smallpox. More recently, Herzog and Rodriguez⁵ reported the finding of perivascular infiltrations of adventitial cells, fibroblasts, lymphocytes, neutrophils and plasma cells in cases of typhus. The neutrophils often predominated. Myocarditis has also been found in cases of Rocky Mountain spotted fever, Lillie⁷ having described the presence of lymphocytes, plasma cells, macrophages and eosinophilic leukocytes. Rickettsia-like bodies have also been recognized (Florman and Hafkenschiel⁴).

From the above it is clear that myocarditis does occur in virus diseases, although it is a rare complication. It may also be emphasized that some of these patients died suddenly (Manca⁸). Histologically, the myocardial lesions were neither uniform nor specific.

Our study is based on a review of the clinical records of 7 patients who died either during the acute stage of poliomyelitis or some time after paralysis of various parts of the body had ensued. In every instance, an attempt was made to rule out a simultaneously present, complicating disease which might have been the cause of the myocarditis. All the hearts were examined microscopically. A varying number of blocks were cut from the myocardium and stained with hematoxylin-eosin, iron-hematoxylin, and according to the Giemsa, Gram, and van Gieson methods. When deemed necessary, the blocks were cut serially.

Clinical Notes. Five of the 7 patients were children, 4, 5, 10, 11 and 14 years old respectively; 2 were adults, 23 and 34 years old respectively.

CASE 1.—A male, aged 34, had contracted the disease 18 days before he died. He had entered the hospital in a paralytic stage and with some respiratory difficulty. He was placed in an oxygen tent, later in a Drinker respirator, and finally was given nasal oxygen. The patient died 10 days later with signs of mid-brain involvement, having developed a temperature of 108°. The autopsy showed, besides the characteristic picture of a poliomyelitis, a severe bronchopneumonia. There was no myocarditis.

Only the most essential data in the clinical courses of the other 6 patients will be briefly summarized.

CASE 2.—A white female, of 4 years, had developed poliomyelitis 5½ months before admission. She had received convalescent poliomyelitis serum, and was admitted to the hospital for physiotherapy for paralysis involving the muscles of the neck and upper and lower extremities. Aside from the paralysis there were no other significant physical or laboratory findings. She did very well until 11 days after admission when she complained of feeling cold. The skin was clammy and she was quite cyanotic. Respiration became labored, the pulse weak and its rate rapid. She was placed in a respirator but became progressively worse and died 6 days later.

CASE 3.—A 5-year-old white male entered the hospital with bulbar poliomyelitis of 2 days' duration. On admission there was paralysis of the palate. The gag reflex was absent and fluid was regurgitated through the nose on attempting to swallow. The lungs and heart presented no abnormal findings. He was given convalescent poliomyelitis serum. The child seemed to improve until 5 days later when he showed signs of cerebral involvement. Cyanosis and respiratory embarrassment ensued, the pulse became rapid and feeble, and the patient expired suddenly.

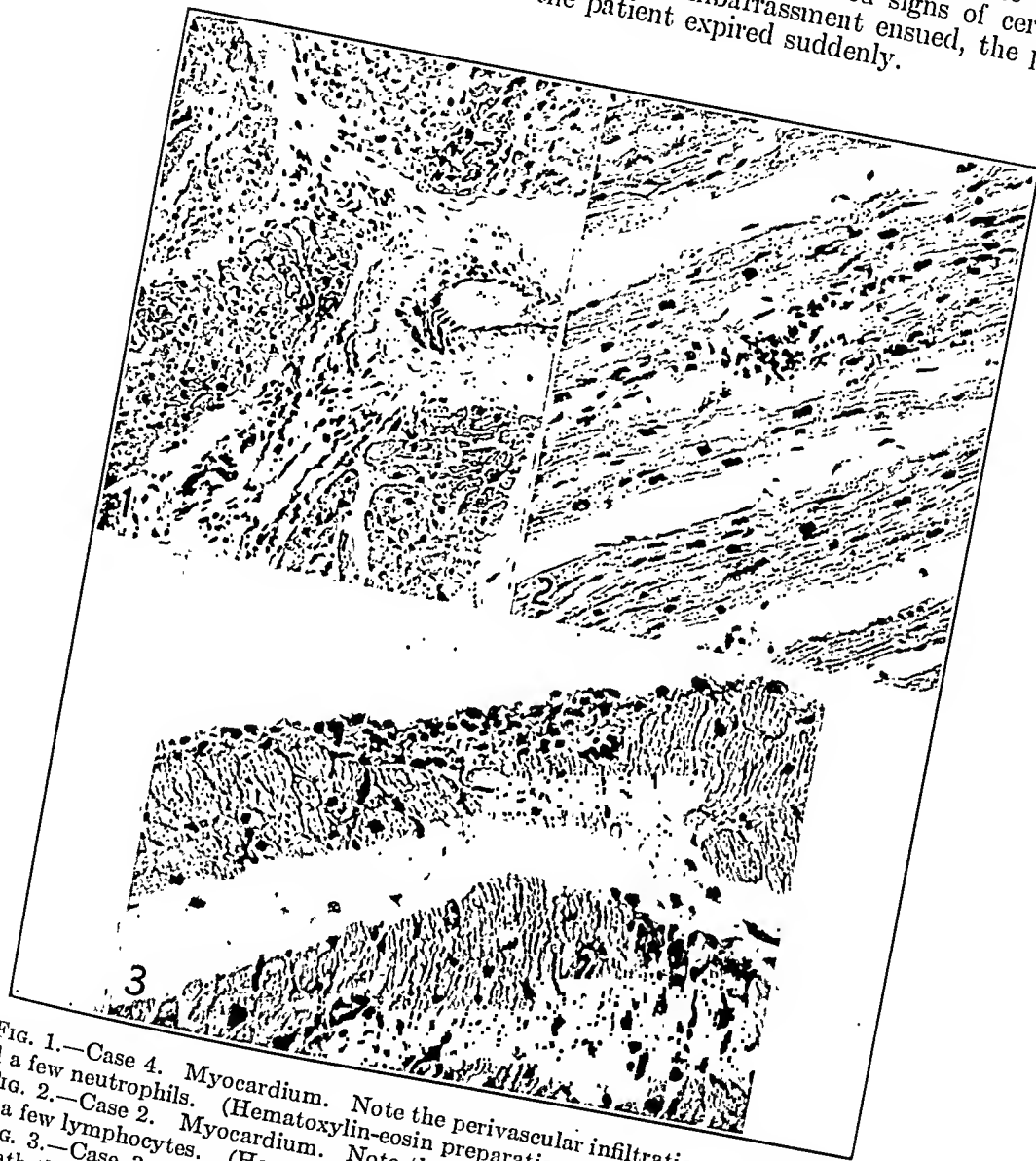


FIG. 1.—Case 4. Myocardium. Note the perivascular infiltration of lymphocytes and a few neutrophils. (Hematoxylin-eosin preparation; $\times 110$.)

FIG. 2.—Case 2. Myocardium. Note the localized accumulations of neutrophils and a few lymphocytes. (Hematoxylin; $\times 150$.)

FIG. 3.—Case 3. Myocardium. Note the accumulations of lymphocytes just beneath the endocardium. (Hematoxylin-eosin; $\times 190$.)

CASE 4.—A 10-year-old white female entered the hospital with bulbar poliomyelitis of 4 days' duration. Convalescent poliomyelitis serum was given but the child's course was steadily downward, and she expired 72 hours after admission.

CASE 5.—A white male, of 11 years, entered the hospital with bulbar poliomyelitis of 2 days' duration. During the ensuing 24 hours the child became progressively worse. The pulse rate dropped to 68 and remained slow for about 12 hours. On the second day following admission the child was quite drowsy and cyanotic and was placed in a respirator. The pulse became very rapid and feeble, and the patient expired 12 hours later.

CASE 6.—A 14-year-old white male entered the hospital with an acute fulminating type of bulbar poliomyelitis of 48 hours' duration. The pulse was thready and rapid. He was placed in a respirator and died suddenly 1 hour after admission.

CASE 7.—A white male, of 23 years, entered the hospital with a diagnosis of poliomyelitis. He was given convalescent serum and placed in a respirator. His condition slowly improved over a period of 5 weeks. At this time the patient suddenly developed a high pulse rate and seemed quite drowsy. Subsequently, he developed some abdominal distress and succumbed rather suddenly.

Pathologic Findings.—The autopsy verified the clinical diagnosis of poliomyelitis in every instance, the relative age of the disease more or less corresponding to the time interval between the clinical onset of the disease and the death of the patient.

The hearts grossly were slightly dilated, but not hypertrophic. Even the hearts of patients who had been for various lengths of time in the Drinker respirator did not disclose any hypertrophy of the right ventricle. The myocardium was slightly flabby, usually grayish-red. No hemorrhage was discernible grossly. Histologically, various changes were manifest. It may be stated that interest in the myocardial changes was first aroused by the finding of inflammatory lesions in the hearts of Cases 3 and 6, and that the changes in the other hearts were found subsequently, after a re-study of the hearts.

Slight inflammatory changes were encountered in the myocardium of Cases 2 and 5. These changes were characterized by a dilatation of capillaries which were filled with neutrophils and perivascular infiltrations. These latter consisted of varying numbers of neutrophils and lymphocytes. In Case 2, in addition to these changes, a few fields showed more diffusely infiltrating inflammatory cells which were still confined to the interstitial spaces and consisted principally of lymphocytes and neutrophils. The myocardial fibers showed varying degrees of cloudy swelling, with a tendency toward coalescence of the fibers. The endocardium was normal. The pericardium in Case 2 showed only a few foci of lymphocytes.

The changes in Cases 3, 6 and 7 were somewhat more severe. Though foci of perivascular infiltrations of neutrophils were still frequently encountered, the principal inflammatory cells were monocytes and cells of the type frequently described as adventitial cells. Often the latter formed typical "collars" around minute blood-vessels. In those fields where the inflammation was more diffuse, the predominating cell was the lymphocyte; a few neutrophils were also seen. In a few instances small foci of lymphocytes, separated

by extravasated red blood corpuscles, were noted just beneath the endocardium. The muscle fibers were occasionally slightly swollen and, in places, had lost their striations. However, in general the individual muscle fibers were well preserved. Occasionally it was noted in the sections of the myocardium that the individual fibers



FIG. 4.—Case 2. Myocardium. Note the coalescence of muscle fibers and the more diffuse infiltration of neutrophils and lymphocytes. (Hematoxylin-eosin; $\times 180$.)

FIG. 5.—Case 6. Myocardium. Note the perivascular infiltration of lymphocytes and a few endothelial leukocytes. (Iron-hematoxylin-eosin; $\times 300$.)

of some of the larger nerve branches which were found adjacent to the branches of the coronary arteries, were spread by an edema-like material. None of the sections of the myocardium showed any bacteria or inclusion bodies.

In summary, the myocarditis as present in these instances of poliomyelitis was characterized by foci of perivascular infiltrations of lymphocytes and neutrophils. Monocytes were also present in some instances, and there was a multiplication of adventitial cells. Occasionally inflammatory cells were seen diffusely invading the interstitial tissues. Minute foci of lymphocytes were also seen just beneath the endocardium. The muscle fibers showed little degenerative change.

Comment. Pathologic evidence of myocarditis of varying degree was found in 6 of 7 instances of poliomyelitis. Clinically, this complication was not suspected.

Although myocarditis may and does occur as the result of various acute infectious processes, the belief is now commonly expressed that with the exception of rheumatic fever, other infectious diseases rarely produce any serious changes in the myocardium. In view of this, it is interesting that in 7 patients dying either in the acute stage or some time after the acute stage of poliomyelitis, pathologic evidence of myocarditis was found in 6 of the cases. This is particularly noteworthy because as far as we have been able to find out, myocarditis in poliomyelitis has received no attention.

There was no correlation between the length of time the disease had existed or the apparent severity of the infection and the degree of myocarditis found.

From a review of these clinical records it is evident that no definite criteria can be laid down for the diagnosis of acute myocarditis in poliomyelitis since it often runs its course without producing any symptoms which may make diagnosis possible.

Although there are no characteristic symptoms, myocarditis may be suspected if the patient suddenly becomes worse and begins to fail rapidly without apparent reason. Often he may become restless and the heart action may be disturbed. Bradycardia may occur but the heart rate is usually rapid and any of the forms of irregularity may appear. The pulse is feeble and reflects the irregularity of the heart. The blood pressure is usually diminished and there may be an increase in the size of the heart. Tachycardia, out of proportion to the temperature, particularly if accompanied by cyanosis, is an early sign that may direct attention to the myocardium during the course of an acute infection. This was present in 3 of our patients. Though some of these symptoms and signs may be associated with poliomyelitis *per se* (Faber³), from this study, myocardial involvement must also be considered.

Because of the extremely high incidence of myocarditis in this series, it is clear that the possible occurrence of myocarditis during the course of poliomyelitis should be borne in mind. The advisability of supportive measures in such cases is imperative.

A number of patients with poliomyelitis, particularly of the bulbar type, die from bronchopneumonia. Among these 7 patients,

4 had pneumonia. In 1 patient (Case 1), the pneumonia was diffuse and in parts organizing. This was the only patient who *did not* have myocarditis. Another patient (Case 4) had a terminal bronchopneumonia, and the others (Cases 2 and 3), an early bronchopneumonia. One patient (Case 6) showed no evidence of pneumonia at autopsy. However, in this patient the most severe myocarditis was found. The question arises as to whether or not the bronchopneumonia in Patients 2, 3 and 4 might have been the source of the myocarditis. In this connection, it must be pointed out that true myocarditis in bronchopneumonia is rather unusual. Among Stone's⁹ cases leukocytic and round cell infiltration was found in 10.8%, and interstitial myocarditis in 2.7%. In our series, Case 1, with the most severe and organizing bronchopneumonia, showed no change in the myocardium and Case 6 with the most severe myocarditis showed no bronchopneumonia. Although from the histologic picture, the bronchopneumonia cannot be ruled out as the possible source of the myocarditis, from the evidence this does not seem to be likely.

The perivascular infiltrations as described above are definitely not characteristic of rheumatic myocarditis. There was no evidence of early fibrinoid deposits. Though the inflammatory cells were often perivascular in distribution, neither the characteristic Aschoff cells nor multinucleated cells were encountered. The histories of these patients also gave no indication of anything that could be interpreted as recent or older attacks of rheumatic fever. From the findings at our disposal a possible coincidental rheumatic myocarditis can easily be ruled out.

It should be pointed out that Herzog and Rodriguez⁵ in their discussion of myocarditis in typhus, described among other cells, the accumulations of adventitial cells around blood-vessels. They also stressed the rarity of degenerative changes. It is interesting that these changes are somewhat similar to those seen in the myocardium of some of our patients with poliomyelitis. Whether or not this indicates that these myocardial changes are characteristic of virus diseases in general cannot be answered at this time. More careful studies of the myocardium of patients dying from virus disease are essential before it can be decided whether or not virus disease causes a definite, clear and characteristic myocarditis.

Patients 3, 6 and 7 died rather suddenly. Patient 6 was ill only 2 days when he suddenly developed pulmonary edema and tachycardia and died 1 hour after having been admitted to the hospital. Patients 3 and 7 seemed to be making good recoveries from poliomyelitis when they suddenly took a "turn for the worse" and succumbed. It is noteworthy that these 3 patients showed the more severe myocarditis. It is possible that the sudden death in these 3 patients may be linked to the myocarditis.

Summary. Seven patients with poliomyelitis are reported, 6 of whom showed evidence at autopsy of varying degrees of myocarditis. Clinically, myocarditis could have been suspected in 3 patients because of a sudden "turn for the worse" without apparent cause, coincident with a rise in pulse rate and cyanosis. The myocarditis was characterized histologically by foci of perivascular infiltrations of lymphocytes and neutrophils. Foci of lymphocytes were also seen just beneath the endocardium. Though the number of inflammatory cells was never very large in any one area, they were present in many blocks cut from different parts of the myocardium. The relation of the myocarditis to the bronchopneumonia which was present in 4 of the 7 patients is discussed. The high incidence of myocarditis in this series warrants the consideration of supportive measures. The sudden death of 3 of these patients may be attributed to the myocarditis.

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AGE, SEX AND RACE RELATIONSHIPS OF AURICULAR FIBRILLATION.

By CURTIS F. GARVIN, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, SCHOOL OF MEDICINE, WESTERN RESERVE UNIVERSITY; VISITING PHYSICIAN, MEDICAL SERVICE, CLEVELAND CITY HOSPITAL, CLEVELAND, OHIO.

(From the Department of Medicine of Cleveland City Hospital and the Western Reserve University School of Medicine.)

THE evidence as to the rôle of age and sex in the etiology of auricular fibrillation is contradictory. Brill¹ states that "the heaviest age incidence is in the third and fourth decades in the valvular group, and in the sixth and seventh decades in the non-valvular group." Lewis² writes that in the non-rheumatic group auricular fibrillation is "related to advancing years" but that in the rheumatic group the incidence "lightens as the years mount." On the other hand, de la Chappelle³ found that "auricular fibrillation in rheumatic heart disease is encountered with greater frequency in persons

past middle life." DeGraff and Lingg⁴ reported that in rheumatic heart disease the "age at death was, on the average, higher when auricular fibrillation existed than when the sinus rhythm was present."

In regard to sex incidence, Stroud, Laplace and Reisinger⁷ were "inclined to believe that auricular fibrillation really predominates significantly in the male." In non-rheumatic autopsied cases in which auricular fibrillation had been present, Brown² found that "males predominated over females in a proportion of two to one." White⁸ likewise found that "the sexes are unequally affected by auricular fibrillation, about twice as many males as females showing this arrhythmia." Cookson,³ on the other hand, discovered exactly the opposite. And finally, DeGraff and Lingg⁴ reported that in rheumatic heart disease, auricular fibrillation occurred with "about equal frequency among males and females."

I have been unable to find any studies in regard to the influence of race upon auricular fibrillation.

This present study of auricular fibrillation is based upon the clinical and pathologic records of 790 consecutive, adult patients who died of heart disease. These cases occurred in 6,548 consecutive postmortem examinations done at Cleveland City Hospital in the decade from January, 1930, to December, 1939, inclusive. Chronic auricular fibrillation was present in 182 cases. The diagnosis of auricular fibrillation was made clinically and was corroborated usually by electrocardiographic findings.

Hypertensive Heart Disease. There were 264 patients who died primarily of hypertensive heart disease. Of these, 207 had a normal cardiac mechanism and 57 had auricular fibrillation. The 207 patients with a normal cardiac mechanism included 144 males (69.6%) and 63 females (30.4%). The 57 patients with auricular fibrillation included 34 males (59.6%) and 23 females (40.4%). The difference is not statistically significant when tested by the chi square method.

The 207 patients with normal cardiac mechanism consisted of 128 white (61.8%) and 79 colored patients (38.2%). The 57 patients with auricular fibrillation included 40 white (70.2%) and 17 colored patients (29.8%). Again the difference is not a significant one.

The age in years at death of the 207 patients with a normal mechanism and of the 57 patients with auricular fibrillation appears in Table 1. The average age at death of the patients with a normal cardiac mechanism was 52.8 years, the standard error being ± 0.83 . The average age at death of the patients with auricular fibrillation was 62.3 years, the standard error being ± 1.4 . The standard error of the difference between these two averages is 1.63. The actual difference, 9.5 years, is 5.8 times this standard error, an indication that the difference is a highly significant one. It appears

that it can be concluded that in fatal hypertensive heart disease, auricular fibrillation is found in the older patients.

TABLE 1.—THE FREQUENCY DISTRIBUTION OF DEATHS OF PATIENTS FROM, 1, HYPERTENSIVE HEART DISEASE WITH NORMAL CARDIAC MECHANISM AND, 2, HYPERTENSIVE HEART DISEASE WITH AURICULAR FIBRILLATION.

Age (yrs.).	Hypertensive heart disease with normal cardiac mechanism.	Hypertensive heart disease with auricular fibrillation.	Total.
15-19	1	..	1
20-24	1	..	1
25-29	2	..	2
30-34	12	..	12
35-39	12	3	15
40-44	20	1	21
45-49	28	1	29
50-54	36	6	42
55-59	33	11	44
60-64	24	8	32
65-69	24	11	35
70-74	9	8	17
75-79	4	7	11
80-84	1	1	2
	<hr/> 207	<hr/> 57	<hr/> 264

Coronary Heart Disease. There were 177 patients who died primarily of coronary heart disease. Of these, 142 had a normal cardiac mechanism and 35 had auricular fibrillation. The 142 patients with a normal cardiac mechanism consisted of 116 males (81.7%) and 26 females (18.3%). The 35 patients with auricular fibrillation included 24 males (68.6%) and 11 females (31.4%), a difference which is not significant.

The 142 patients with a normal cardiac mechanism included 124 white (87.3%) and 18 colored persons (12.7%). The 35 patients with auricular fibrillation were white in 34 instances (97.1%) and colored in 1 instance (2.9%). This difference is not significant.

The age in years at death of the 142 coronary patients with a normal cardiac mechanism and the 35 patients with auricular fibrillation appears in Table 2. The average for those with normal cardiac mechanism was 59.8 years (standard error ± 0.96). For those with auricular fibrillation it was 69.1 years (standard error ± 1.6). The standard error of the difference between these two averages is 1.87. The actual difference, 9.3 years, is 4.97 times this standard error, an indication that the difference is a highly significant one. Accordingly, it would seem that, on the average, in fatal coronary heart disease, patients with auricular fibrillation are apt to be older than those with a normal cardiac mechanism.

Rheumatic Heart Disease. There were 119 patients who died primarily of rheumatic heart disease; 58 had a normal cardiac mechanism and 61 had auricular fibrillation. The 58 patients with a normal cardiac mechanism included 33 males (56.9%) and 25 females (43.1%). The 61 with auricular fibrillation included 36 males (59%) and 25 females (41%), a difference which is not significant.

TABLE 2.—THE FREQUENCY DISTRIBUTION OF DEATHS FROM, 1, CORONARY HEART DISEASE WITH NORMAL CARDIAC MECHANISM AND, 2, CORONARY HEART DISEASE WITH AURICULAR FIBRILLATION.

Age (yrs.).	Coronary heart disease with normal cardiac mechanism.	Coronary heart disease with auric- ular fibrillation.	Total.
30-34	2	..	2
35-39	4	..	4
40-44	8	..	8
45-49	16	..	16
50-54	13	2	15
55-59	28	6	34
60-64	14	2	16
65-69	29	7	36
70-74	15	7	22
75-79	7	6	13
80-84	5	3	8
85-89	1	2	3
	<hr/> 142	<hr/> 35	<hr/> 177

The 58 with normal mechanism included 47 white (81%) and 11 colored patients (19%). The 61 with auricular fibrillation consisted of 56 white (91.8%) and 5 colored patients (8.2%). This difference also is not significant.

TABLE 3.—THE FREQUENCY DISTRIBUTION OF DEATHS FROM, 1, RHEUMATIC HEART DISEASE WITH NORMAL CARDIAC MECHANISM AND, 2, RHEUMATIC HEART DISEASE WITH AURICULAR FIBRILLATION.

Age (yrs.).	Rheumatic heart disease with normal cardiac mechanism.	Rheumatic heart disease with auric- ular fibrillation.	Total.
10-14	3	..	3
15-19	7	5	12
20-24	4	0	4
25-29	5	4	9
30-34	6	2	8
35-39	9	10	19
40-44	3	9	12
45-49	3	9	12
50-54	5	12	17
55-59	5	3	8
60-64	5	4	9
65-69	2	2	4
70-74	1	1	2
	<hr/> 58	<hr/> 61	<hr/> 119

The average age at death of the 58 patients with normal mechanism and the 61 with auricular fibrillation appears in Table 3. The average for the former was 38.4 years (standard error ± 2.17), for the latter 44.2 years (standard error ± 1.66). The standard error of the difference between these two averages is 2.7. The actual difference, 5.8 years, is 2.1 times this standard error, an indication that the difference is probably a significant one. Thus it can be concluded that in fatal rheumatic heart disease, as in fatal hypertensive and coronary heart disease, auricular fibrillation is found in older patients, while a normal cardiac mechanism usually is encountered in younger patients.

Summary. The average age at death of 207 patients with hypertensive heart disease and a normal cardiac mechanism was 52.8 years, of 57 patients with hypertensive heart disease and auricular fibrillation 62.3 years. Patients with coronary heart disease and a normal cardiac mechanism (142) averaged 59.8 years at death; 35 patients with coronary heart disease and auricular fibrillation averaged 69.1 years. Fifty-eight patients with rheumatic heart disease and a normal mechanism died at an average age of 38.4 years; 61 who had rheumatic heart disease and auricular fibrillation died at an average age of 44.2 years. All these differences seem to be statistically significant. It would appear that the average age at death of cardiac patients with auricular fibrillation is greater than the average age of cardiac patients with a normal cardiac mechanism.

No association between auricular fibrillation and sex or race was demonstrable.

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CORONARY THROMBOSIS IN A YOUNG DIABETIC.

BY NORMAN REITMAN, B.S., M.D.,*

ASSISTANT PHYSICIAN,

W. RUSSELL GREENWOOD, B.S., M.S., M.D.,†

DIRECTOR,

AND

JOSEPH H. KLER, B.A., M.D.,

ASSOCIATE DIRECTOR, DEPARTMENT OF STUDENT HEALTH, RUTGERS UNIVERSITY,
NEW BRUNSWICK, N. J.

(From the Department of Student Health, Rutgers University.)

CORONARY disease has been regarded as an affliction of the declining years of life. Like all disease concepts, however, we are learning more and more that these so-called degenerative diseases can occur

* Associate Cardiologist, St. Peter's General Hospital, New Brunswick; Clinical Assistant in Medicine (Cardiology), New York University College of Medicine Clinic, New York City.

† Associate Professor of Physiology, Rutgers University, New Brunswick, N. J.

in the earlier age groups. The literature contains an increasing number of case reports of coronary artery sclerosis and thrombosis occurring under 40 years of age.

In this paper we are reporting a definite case of coronary artery thrombosis in a diabetic youth of 20 years, with a brief review of the literature emphasizing the relation between the abnormal cholesterol levels found in diabetes and the premature onset of coronary artery sclerosis.

Case Report. The patient, J. D., a 20-year-old junior at Rutgers University, was first seen in the office of the University Physician on May 30, 1939, complaining of precordial pressure and dyspnea. The patient has been a diabetic since the age of 9. He is now controlled with diet and protamine insulin. Although the patient occasionally had slight episodes of hypoglycemia on regular insulin he has been symptom-free on protamine. He had never experienced precordial pain, dyspnea, orthopnea or other evidence of congestive or anginal failure. Past history otherwise was negative.

Two days before, the patient had gone swimming and had to swim some distance to reach shore. He then noticed that the dyspnea, which was present, remained for a much longer time than usual. However, he had no other complaints at that time. Two days later he began to notice a sense of discomfort, described as pressure, over his precordium and also dyspnea on slight exertion. This pressure did not radiate, was constant, and appeared to be aggravated after eating and exercise. No weakness, sweating or other signs of shock were present. The symptoms persisted and the patient reported to the Student Health Office.

Examination revealed no evidence of any acute illness. The only suspicious findings were referable to the heart. It was not enlarged, the P.M.I. being in the fifth intercostal space at the mid-clavicular line. The sounds were of fair quality. A soft systolic murmur was heard over the mitral area. This was not transmitted. No thrill, gallop or friction rub was heard. The ventricular rate was 88 per minute, regular sinus rhythm, A2 > P2. All other findings were negative save the eyegrounds which showed early tortuosity of the vessels with moderate atherosclerotic changes in the arteries. Blood pressure was 120/74. Urine examination revealed a trace of sugar but was otherwise negative. White blood count was normal. An electrocardiogram revealed evidence of acute myocardial infarction involving the posterior surface of the left ventricle.

The patient was advised to go to bed, but as it was the end of the school year he returned home for the summer vacation. For the first month at home he was in bed under the care of his family physician and we did not have an opportunity to get in touch with him until the opening of college in September, 1939. At this time he appeared to have suffered no adverse effects from his illness. He had worked as a clerk during the summer, and had engaged in golf as a form of exercise. He had noticed, however, that after playing one or two holes he had to stop because of a sense of substernal pressure which did not radiate, but was relieved by rest. Once or twice these attacks were accompanied by dizziness. Lately he noticed a return of this substernal oppression immediately after eating, disappearing spontaneously within $\frac{1}{2}$ hour. He never had any gastro-intestinal complaints prior to this episode.

Examination revealed a slight enlargement of the heart to the left. The P.M.I. was outside the mid-clavicular line. The first apical sound was muffled and of poor quality. The systolic mitral murmur had become more pronounced and harsh. There were no other thrills or murmurs.

The ventricular rate was 80 per minute, regular sinus rhythm, A2 > P2. Blood pressure 116/72. Roentgenologic examination of chest showed moderate enlargement of left ventricle. Electrocardiographic examination at this time revealed regressive changes which were interpreted as evidence of healing.

The patient was allowed to continue school and engage in sedentary activities but was warned about overtaking himself. Reexamination in January, 1940, revealed still further regression in the electrocardiographic pattern. The patient was asymptomatic at the last time seen, save for occasional precordial pressure after eating too much.

A blood cholesterol test taken in January, 1940, revealed 350 mg. per 100 cc. with blood sugar of 100 mg. per 100 cc. Studies of the cholesterol fractions revealed a normal ratio.

Surveying the literature on coronary thrombosis under the age of 40, we found a total of 221 cases. In this group 34 cases were below 30 and 4 were below 20 years of age. The incidence of this young group to the incidence of coronary thrombosis in general varies between 1% and 9%. White⁹ found 3% of 418 cases under 40. In Conner and Holt's series of 287 cases, 8% were under 40 and 1% under 30.

Our case is the fifth youngest to be reported with electrocardiographic findings. Sprague and Orgaine⁸ describe 2 cases at 15 and 16 years proven at necropsy. The next youngest cases diagnosed clinically were a boy of 18 reported by Jamison and Hauser³ and a woman of 20 reported by May.⁵ In our case, the elevated blood cholesterol suggested an abnormality in cholesterol metabolism, found frequently in diabetes, as the cause of premature coronary sclerosis.

The relationship of abnormal cholesterol metabolism to diabetes has long been known to be a close one. In the days of high fat diabetic diets it was quite usual to find hypercholesterolemia. Today, however, this is not seen save in uncontrolled diabetics. Rabinowitch⁶ believes that the blood cholesterol is more important than the blood sugar in the control of diabetes. He believes a hypercholesterolemia is one of the earliest signs of acidosis and never regards a diabetic as under control until the blood cholesterol is normal. There have been isolated case reports in the literature of diabetics who have died of coronary disease at a young age where the blood cholesterol reached extreme heights. Such a case was reported by Cullinan and Graham.² A 27-year-old diabetic on a low carbohydrate, high fat diet developed precordial pain, fever and leukocytosis. The electrocardiogram suggestive of infarction of the anterior wall was confirmed at necropsy. There was severe atheromatosis in this patient. The cholesterol content of the dried aorta was 5.86% in comparison to a control with a value of 0.64%.

The imbibition theory of arteriosclerosis, introduced by Virchow and modified by Aschoff,¹ may or may not be the correct theory but

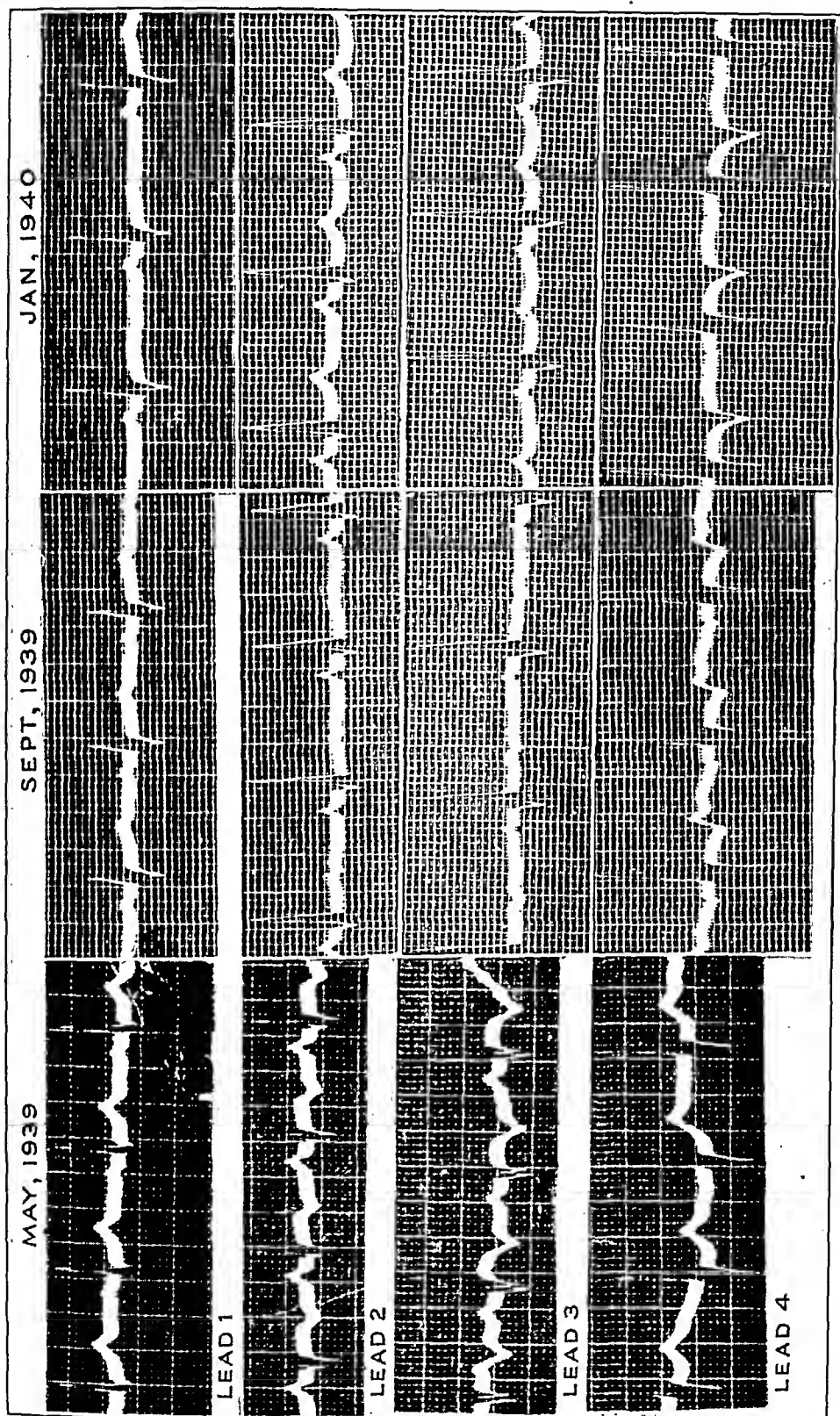


Fig. 1.—Electrocardiograms during and after myocardial infarction (post. left vent.).

it certainly applies to the conditions met in diabetes. Here we have the arteriosclerotic process accelerated and the presence of a high blood cholesterol, which Aschoff was the first to emphasize, playing a fundamental rôle in the pathogenesis of atherosclerosis. As Leary^{4a,b} has shown, the atherosclerotic process can begin in the young as well as the old, and in young diabetics with hypercholesterolemia, it is easy to see why marked atheromatous changes occur. As a rule the vessels most subject to these changes are those under the greatest physiologic strain and for that reason the coronary vessels are among those most frequently involved, chiefly the anterior descending branch of the left coronary artery.

Root and Sharkey,⁷ in a study of 175 cases of diabetes which came to necropsy, found the coronary arteries to be the most common site of arteriosclerosis in over 75% of the cases. Severe coronary disease was found in 47% with coronary thrombosis in 20%, whereas in the control group severe coronary disease was found in 13% with only 2% showing coronary thrombosis. An interesting conclusion from the above study was that arteriosclerosis was related to the duration of the diabetes rather than the age of the patient or the severity of the diabetes. No coronary sclerosis was found in any diabetic of less than 5 years' duration, regardless of the severity. Further, in the group under 40 years of age, the incidence of arteriosclerosis in diabetes of short duration was no higher than in non-diabetics. Further perusal of the literature shows this to be a constant finding. Another statistical fact which supports this belief is that the incidence of the anginal syndrome triples in the second decade of diabetes but not before.

These excerpts from the literature further stress the intimate relationship between diabetes, abnormal cholesterol metabolism and early onset of coronary sclerosis. Further studies along such lines are indicated to clarify these problems.

Summary. 1. A case of coronary thrombosis in a diabetic youth of 20 years is presented.

2. The relationship of cholesterol metabolism to diabetes and the premature onset of coronary disease is briefly discussed.

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A CASE OF BRUCELLA ENDOCARDITIS WITH CLINICAL, BACTERIOLOGIC, AND PATHOLOGIC FINDINGS.*

By WESLEY W. SPINK, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, UNIVERSITY OF MINNESOTA MEDICAL SCHOOL,

LEONARD A. TITRUD, M.D.,

NATIONAL CANCER FELLOW, DEPARTMENT OF SURGERY, UNIVERSITY OF MINNESOTA MEDICAL SCHOOL,

AND

PAUL KABLER, M.D.,

ASSISTANT CHIEF OF LABORATORIES, DIVISION OF PREVENTABLE DISEASES,
MINNESOTA DEPARTMENT OF HEALTH,
MINNEAPOLIS, MINN.

(From the Divisions of Internal Medicine and Pathology of the University of Minnesota Hospitals and Medical School, and the Division of Preventable Diseases of the Minnesota Department of Health.)

WE are presenting the clinical, bacteriologic and pathologic findings in the second proved case of brucella endocarditis treated at the University Hospitals. The first case was reported in 1939 with a review of the literature.³ Since then, Smith and Curtis¹ have also recorded a case.

Case Report. W. M., a 36-year-old white male farmer, entered the University Hospitals on September 4, 1940, after an illness of 3 weeks' duration. He complained of daily chills, and fever, drenching sweats, weakness and loss of weight. He had had rheumatic fever 20 years previously and was told subsequently that he had "leakage of the heart."

While being examined, he had an attack of syncope, which was followed by aphasia and a flaccid paralysis of the right arm and leg. He was well developed and nourished. The pulse rate was 84 per minute and regular; temperature, 98.6° F., respiratory rate 20 per minute; blood pressure 120/75. Eyes: there was a ptosis of the left lid; at rest, the left eye looked downward and out; the left pupil was larger than the right, but both reacted to light and accommodation; no petechiæ were seen in the conjunctivæ; the fundi appeared normal. Mouth: the jaw deviated to the left; the tongue protruded to the right; the teeth were carious. Lungs: clear. Heart: the apical impulse was visible in the sixth interspace in the anterior axillary line; no definite thrills were palpable; on auscultation the sounds were regular and of good quality; at the apex a blowing systolic murmur was audible, and was transmitted to the left axilla; in the second right interspace, a systolic murmur was present, which was transmitted into the neck vessels; a diastolic murmur was also heard in this area, which reached its maximum intensity in the third and fourth interspaces at the left sternal border; the second pulmonic sound was loud and snapping. Abdomen: the liver edge was palpable 2 cm. below the costal margin; the lower border of the spleen was palpated at the costal margin.

Initial laboratory data included the following: urinalysis normal; hemoglobin 11.4 gm.; leukocytes 6000 cells per c.mm., with 75% neutrophils, 22% lymphocytes, and 3% monocytes; serologic tests of the blood serum

* Presented before the Minnesota Society of Internal Medicine, Minneapolis, May 24, 1941.

for syphilis were negative; the sedimentation rate of the erythrocytes was 47 mm. in the first hour and 70 mm. in the second hour (Westergren).

It was the consensus that the patient had aortic stenosis and regurgitation, and very likely mitral stenosis and regurgitation. The basic valvular lesions were thought to be of rheumatic origin with bacterial vegetations superimposed upon the healed valvulitis.

Course and Treatment. The patient continued to have daily chills with a maximum rise in his temperature of 102° to 104°. Six cultures of venous blood made during the first 16 hospital days remained sterile. Complete examination of cerebrospinal fluid was within normal limits. Nineteen urinalyses were normal. Two weeks after entry, agglutinins for *B. melitensis* var. *abortus* were present in the serum on 4 occasions in a titer of 1 to 1280. An intradermal test with brucella antigen showed no reaction and was performed after the results of the agglutination test were known. A total of eight samples of venous blood were obtained over a period of 9 weeks. *Brucella* of the *abortus* type was isolated from 7 of these 8 specimens. It was later learned that the patient's cattle had Bang's disease and he had consumed raw milk from this source.

He was given sulfathiazole, receiving a total of 31 gm. in 6 days. The blood concentration of sulfathiazole was 3 to 4 mg. per 100 cc. This therapy had no effect upon his clinical course or the bacteremia. On the twenty-sixth day of hospitalization, sulfanilamide therapy was instituted. He received a total of 67 gm. over a period of 12 days with blood levels of 7 to 11 mg. per 100 cc. being sustained. Coincident with the exhibition of sulfanilamide, there was a general improvement in his condition but *brucella* were still isolated from his blood during this period. Following the discontinuance of chemotherapy, the patient's temperature began to rise. On two subsequent occasions, he again received sulfanilamide. During one period of 19 days he received 108 gm. with coincident clinical improvement. At another period, 61 gm. were given over a period of 11 days, this time without clinical improvement. He became progressively more dyspneic, cyanotic, and signs of pulmonary edema appeared. He expired on the ninety-first day after entry to the hospital.

NECROPSY. Gross Findings. Peritoneum: No evidence of peritonitis or ascites. Pleural cavities: firm, fibrous adhesions at both apical regions. The right pleural cavity contained 2 liters of a straw-colored fluid and the left cavity had 1 liter of a similar fluid. Pericardial sac: walls glistening with 300 cc. of a straw-colored fluid present. Heart: weight 625 gm. The musculature was firm. There was a dilatation of all the chambers with a definite hypertrophy of the wall of the left ventricle. There were no thrombi present, and there was no evidence of myocardial fibrosis. The pulmonary valve appeared normal. The tricuspid and mitral valves were dilated. The diameter of the mitral valve was 2.25 cm. The chordæ tendinæ were thickened and shortened. There was a definite nodular, fibrous thickening of the edges of the mitral valve representing a healed valvulitis. About three-fourths of the entire periphery of the mitral valve was covered by large, irregular, friable, brownish-red vegetations. The vegetations were mainly on the atrial side of the mitral valve, and had caused an erosion 1 cm. in diameter through one leaflet. The chordæ tendinæ were also covered with vegetations. The aortic valve was stenotic with the diameter of its aperture being 1.5 cm. The edges of the leaflets were thickened by a nodular and fibrous tissue change. Some of the nodules contained calcium. The coronary arteries appeared normal. Lungs: the right weighed 1150, and the left 800 gm. There was a marked and generalized congestion of the substance of both lungs. The right upper lobe, particularly the superior one-half, was consolidated. On section, this lobe varied from a gray appearance to a reddish discoloration. Purulent

exudate was present in the lung substance and could be expressed from the smaller bronchi. Spleen: weight 650 gm. The organ was soft, red, and congested with two large infarcts present. Liver: weight 1800 gm. Firm and possessed a nutmeg appearance. Kidneys: each weighed 200 gm. Cloudy swelling apparent. Capsules were markedly adherent with evidence of old infarction present. Brain: there was an area of softening occupying the cortex of the left temporal and postero-inferior portion of the frontal lobe. The lumen of the left middle cerebral artery was almost pinpoint in size shortly after its origin from the internal carotid artery.

Microscopic Findings. Heart: there was a diffuse infiltration of lymphocytes with occasional neutrophils in the connective tissue adjacent to the muscle fibers. Within the connective tissue surrounding the small arteries, there were accumulations of similar types of cells. These inflammatory foci had the appearance of Aschoff nodules. The entire section represented a subacute myocarditis. Some of the small arteries were partially occluded by homogenous eosin-staining bodies resembling emboli. The coronary arteries were within normal limits. The aortic leaflet possessed a fibrous nodular thickening and was essentially acellular. The mitral valve was also the site of a fibrous nodular thickening. An area of calcification was apparent in the middle of the leaflet. Loosely attached to the surface of the mitral leaflet was a large irregular vegetation composed of loose fibrous tissue containing numerous neutrophils, lymphocytes, and fibroblasts. A great portion of the vegetation was composed of amorphous eosin-staining protein representing cellular debris, platelet thrombi and bacteria. Lungs: sections from the consolidated portion revealed an extensive atelectasis. The exudate in the walls of the compressed alveoli consisted mostly of mononuclear cells such as macrophages and lymphocytes, with a scattering of neutrophils. Several sections from other parts of the lung showed only a few dilated alveoli. Some alveoli were congested with numerous erythrocytes; large macrophages containing brown granules; and partially filled with coagulated eosin-staining serum. Pleuræ: Both were thickened and replaced by an acellular fibrous layer. Liver: there was a marked engorgement of the sinusoids at the centers of the lobules with erythrocytes, and distention of the central veins. A moderate atrophy of the central liver cords had occurred. Dark brown granules were present in the central liver cells. A few neutrophils were present in the center of the lobules. A diffuse mild fatty metamorphosis had taken place. Kidneys (hematoxylin-eosin and azo-carmin stains): glomeruli were enlarged and very cellular. Most of the cells were mononuclear leukocytes. The capillary basement membrane was swollen. There was a minimal intimal atherosclerosis of the small arteries. Lymph nodes from the hilar region: there was a generalized increase of reticulum. Numerous large macrophages were filled with hemosiderin granules. Spleen: a moderate congestion with erythrocytes was present. A reticular hyperplasia was apparent with occasional large mononuclear cells seen in the sinusoids. There were only a few neutrophils. A mild fibrosis of the pulp was apparent. Brain: the lumen of the left middle cerebral artery was almost completely occluded by a thickened intima composed of proliferating fibroblasts and prominent capillaries. The elastic lamina was prominent. No inflammatory reaction was apparent. Extensive areas of cerebral tissue were replaced by fat granule cells.

Bacteriologic Data. Blood cultures: bacto tryptose broth with 1% sodium citrate was used. Venous blood (5 cc.) was introduced into 25 cc. of the broth contained in large vaccine bottles. Under sterile precautions, 10% of the air in the bottles was replaced by carbon dioxide. Incubation was then carried out for 5 days at 37° C. Subcultures were made at the end of 5 and 15 days on dextrose agar slopes which were also incubated in

the presence of increased carbon dioxide tension. Organisms isolated in this manner proved to be Gram-negative, pleomorphic bacilli, growing only in the presence of increased carbon dioxide tension. The organisms did not ferment dextrose, saccharose, lactose, or mannite, and were agglutinated in high titer by antibrucella serum. Spinal fluid: no organisms were isolated from the cerebrospinal fluid obtained on eighth hospital day. Necropsy material: smears were made upon glass slides directly from the soft vegetations of the mitral valve and stained by Gram's method. Microscopic examination revealed myriads of Gram-negative, pleomorphic bacilli having the morphologic appearance of brucella. Specimens of pericardial and pleural fluid and heart's blood were added to tryptose broth. After 5 days of incubation, subcultures were made on dextrose agar slopes and at the same time a portion of the cultured fluids was injected intraperitoneally into guinea pigs.

Fresh sections of spleen, liver, valve vegetation, hilar lymph nodes and lung were macerated in sterile physiologic sodium chloride solution, and then added to tryptose broth. After 5 days of incubation, dextrose agar slants were inoculated and material injected into guinea pigs. The animals were sacrificed at the end of 4 weeks. Under sterile precautions, sections of the animals' spleens were smeared on dextrose agar slopes and the latter incubated. Fermentation and agglutination studies were carried out with suspected organisms isolated from each animal. The results of the post-mortem bacteriologic studies are presented in Table 1.

The final diagnoses were: brucellosis; subacute brucella endocarditis; subacute myocarditis; old rheumatic heart disease with mitral stenosis and aortic stenosis and regurgitation; embolism to left middle cerebral artery and left parietal encephalomalacia; mononuclear pneumonia; pulmonary edema and congestion; infarction of the kidneys and spleen; subclinical glomerulonephritis.

TABLE 1.—RESULTS OF POSTMORTEM BACTERIOLOGIC STUDIES.

Specimen.	Dextrose agar.	Tryptose broth.	Guinea pigs.
Spleen	<i>Br. abortus</i>	<i>S. albus</i>	<i>Br. abortus</i> *
Liver	<i>Br. abortus</i>	<i>S. albus</i>	<i>Br. abortus</i>
Heart vegetation	<i>Br. abortus</i>	<i>Br. abortus</i>	<i>Br. abortus</i>
Hilar lymph nodes	<i>S. albus</i>	<i>S. albus</i>	<i>Br. abortus</i>
Lung	<i>S. albus</i>	<i>S. albus</i>	<i>Br. abortus</i>
Pericardial fluid	<i>Br. abortus</i>	<i>S. albus</i>	<i>Br. abortus</i>
Pleural fluid	<i>S. albus</i>	<i>S. albus</i>	No growth†
Heart's blood	<i>Br. abortus</i>	<i>Br. abortus</i>	<i>Br. abortus</i>

* Guinea pig inoculated with suspension of spleen December 4, 1940; died December 31, 1940. Cultures of spleen from this animal were overgrown with staphylococci and spore-formers. *Br. abortus* was isolated from the spleen of a guinea pig inoculated December 9, 1940, with a portion of culture in tryptose broth.

† In addition to the animal inoculated directly with pleural fluid, a guinea pig was inoculated December 9, 1940, with a culture of pleural fluid in tryptose broth. *Br. abortus* was not found in either of these animals.

Comment. This report emphasizes the necessity of using special cultural methods in order to prove the diagnosis of brucellosis.

Another point of interest is the type of cellular infiltration which was noted in the lungs and kidneys. The exudate was composed for the most part of mononuclear cells rather than neutrophils. Another feature was the tissue change apparent in the myocardium. It was not unlike that seen in acute rheumatic fever. We have no reason to believe that the patient had acute rheumatic fever in addition to his brucella infection.

Finally, therapy with sulfathiazole and sulfanilamide had no effect upon the patient's bacteremia. Administration of the latter drug coincided with only temporary improvement in the patient's condition. We have successfully treated 3 patients with sulfanilamide having a brucella bacteremia without endocarditis. As we have pointed out elsewhere,² treatment of any bacterial endocarditis with the sulfonamide compounds is accompanied by disappointing results because of the very nature of the focus of infection.

Summary. 1. The clinical, pathologic, and bacteriologic data are detailed for a patient with brucella endocarditis.

2. The patient received a total of 31 gm. of sulfathiazole and 236 gm. of sulfanilamide. This therapy had no effect upon the bacteremia, and only temporary clinical improvement was observed.

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PERSISTENT TACHYCARDIA AND PULSE-TEMPERATURE DISPROPORTION: RELATION TO ACUTE MYOCARDIAL LESIONS.

BY JAMES R. LISA, M.D.,
PATHOLOGIST,

CYRIL SOLOMON, M.D.,
FORMER RESIDENT PATHOLOGIST,

AND

DAVID ECKSTEIN, M.D.,
RESIDENT PHYSICIAN, FIRST MEDICAL DIVISION,
NEW YORK, N. Y.

(From the City Hospital, Welfare Island, Department of Hospitals.)

It has long been known that the pulse during sleep is slower than during waking hours. It has also long been known that acceleration occurs with cardiac insufficiency and that this acceleration persists during sleeping hours. This fact has been employed particularly in the study of the rheumatic heart^{2,4,5} and in coronary artery disease. It has likewise been established that in fevers, for each degree of temperature above normal, a rise in the pulse rate of 8 to 10 points can be expected.^{2,4} The mechanism producing the abnormal acceleration of the rate has remained obscure. As far back as 1914, Mackenzie raised the question whether it was caused by a myocardial lesion, by nerve stimulation from inflamed tissue or by increased irritability of the cardiac muscle. During the past several years, it has been frequently observed that pathologic conditions are present in the heart in cases displaying a tachycardia out of proportion to the temperature when cardiac disease may or

may not have been the prominent feature of the clinical syndrome. This observation led us to study a group of such cases.

In 100 hearts from cases having a persistent tachycardia and discrepancy between the rate of the pulse and the height of the temperature, demonstrable acute injury to the myocardium was found in 81. In 98 cases in which the discrepancy was lacking, the number of instances with acute myocardial changes was 21. These observations suggest that the relationship between the pulse and temperature offers a valuable clinical guide to the presence or absence of myocardial disease.

Only those cases were chosen for analysis in which the discrepancy was present for 48 hours or more and persisted both day and night. Certain types of cases were eliminated from consideration, auricular fibrillation, acute massive non-cerebral hemorrhage, hyperthyroidism, surgical shock and infants. The arrhythmia prevents the development of the phenomenon in the first and tachycardia is a natural result in the others. Infants present a problem which deserves separate study. The control cases also were chosen only if under observation 48 hours or more. Although the time limit set in the choice of material prevented the use of strictly consecutive cases, all necropsies were performed within the past 2½ years.

The ages ranged from 11 to 83 years. There were 51 men and 49 women. The blood pressure of 58 patients was within normal limits; of 12, slightly raised (140-170 systolic, 90-100 diastolic); of 14, moderately high (170-200 systolic, 100-140 diastolic); and of 8, very high (200 systolic, 140 diastolic or greater).

The weights of the test hearts were on an average not much increased. Sixty-two weighed less than 400 gm., 30 between 400-600 gm., 4 over 600 gm.; 4 were not weighed.

Coronary sclerosis was present in about half the cases. It was marked in 18, moderate in 26, slight in 16 and absent in 40.

The gross necropsy findings in 36 of the hearts were acute infarction of the myocardium with or without thrombosis, 14; rheumatic heart disease, 6; metastatic carcinoma, 6; acute endocarditis, 4; acute pericarditis, 4; syphilitic aortitis and valvulitis, 2. One case of acute endocarditis was superimposed on a healed rheumatic deformity, another on a congenital lesion. One of the metastatic tumors had acute pericarditis.

The histological findings were much more revealing. Of the 6 rheumatic hearts, acute rheumatic myocarditis was present in 4, twice complicated with acute non-rheumatic endo- and myocarditis. Two cases had only the superadded non-rheumatic myocarditis. Two other cases were discovered with many Aschoff bodies and normal valves. All the cases of acute pericarditis and acute endocarditis had associated acute myocardial lesions. In the 2 syphilitics, a chronic granulomatous lesion possibly syphilitic was present in 1 and an acute interstitial myocarditis in the other.

In the remaining 43 cases, an acute myocarditis with polymorphonuclear reaction was present in 22, acute miliary infarcts in 10, acute miliary necrosis in 4, marked fragmentation without cellular response in 4, tuberculosis in 2, and multiple abscesses in 1.

Cardiac symptomatology dominated the clinical features in 29 cases. These were the 4 acute endocarditides, the 2 syphilitic aortitis and valvulitis, 9 of the acute massive infarctions, 3 of the rheumatics, 4 each of the acute myocarditides and miliary infarctions, and 1 each of pericarditis, miliary necrosis and metastatic carcinoma. The last case was of peculiar interest. The clinical diagnosis was acute coronary thrombosis; the bronchogenic carcinoma was entirely unsuspected.

Cardiac symptoms were absent or a very minor clinical feature in 52. Pyelonephritis was the most frequent complication found

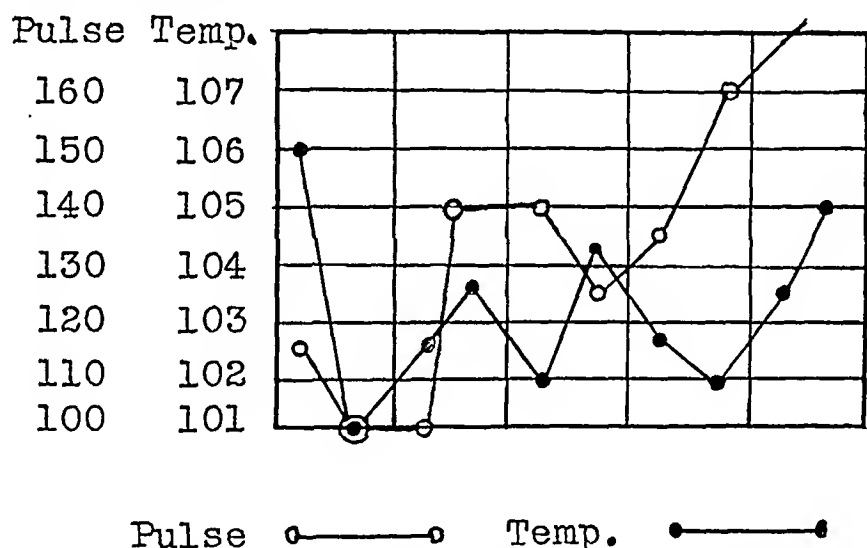


FIG. 1.—Case of lobar pneumonia complicated with acute pericarditis and myocarditis.

at necropsy, being present in 12, the acute pneumonias and pulmonary infections with bronchogenic carcinoma next in 8, and pulmonary tuberculosis in 5. Other infectious processes were present in most of the remainder. The most common of the cardiac conditions were acute myocarditis and miliary infarcts.

Demonstrable lesions of the myocardium were absent in 19 cases. The anatomic diagnoses were pulmonary tuberculosis, 5; pneumoconiosis, 1; thrombosis of the inferior vena cava and its tributaries, 3; intestinal obstruction, 4; chronic pyelonephritis, 2; hepatic cirrhosis, 2; chronic ulcerative colitis, 1; brain tumor, 1. One case of pyelonephritis presented clinically as a cardiac case.

The control group without a disproportion of pulse and temperature consisted of 98 cases. The ages ranged from 29 to 94 years. Normal blood pressures were found in 38, slightly raised in 12, moderately raised in 17, and very high in 10. It was not recorded in 21.

There were 65 men and 33 women. Cardiac hypertrophy was more marked, although half the cases (44) had hearts weighing less than 400 gm.; 42 weighed between 400 and 600 gm., and 8 weighed 600 gm. or more. The weights of 4 were not recorded. Severe coronary sclerosis also was more prominent. Marked arteriosclerosis was present in 28, moderate in 20, slight or absent in 50.

Acute myocardial lesions were present in 19 hearts. They were acute coronary thrombosis, 2; acute miliary infarctions, 5; interstitial myocarditis, 7, 3 with pericarditis; miliary abscesses, 3; tuberculous pericarditis, 1; and atypical Aschoff bodies, 1. Two hearts had chronic lesions, chronic granulomatous myocarditis and amyloidosis.

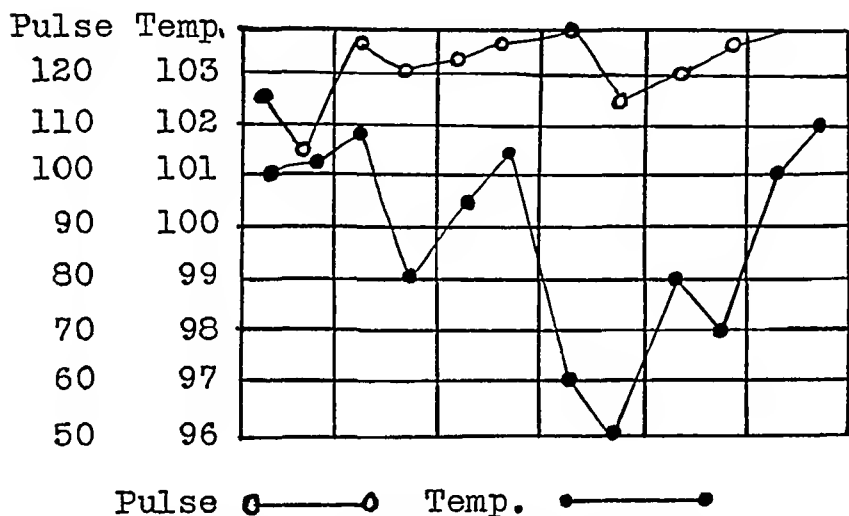


FIG. 2.—Case of severe pyelonephritis, uremia, acute pericarditis, and acute myocardial infarction.

Cardiac symptoms, almost invariably of hypertensive character, dominated the clinical picture in 14 instances. Eight had acute myocardial lesion, acute coronary thrombosis, 2; tuberculous pericarditis, 1; miliary infarctions, 3; interstitial myocarditis, 2.

The associated lesions in the 13 non-cardiac cases with myocardial lesions showed some similarity to the series with the phenomenon of pulse-temperature disproportion. The anatomic diagnoses were pyelonephritis, 3; pulmonary embolism, 3; 1 each of cerebral thrombosis, cerebral hemorrhage, pulmonary tuberculosis, staphylococcal septicemia, bronchogenic carcinoma, carcinoma of the esophagus and amyloidosis. In the case of pulmonary tuberculosis, atypical Aschoff bodies of the myocardium were found. The myocardial abscesses were found in 1 case of pyelonephritis with prostatic abscess, the staphylococcal septicemia and a cerebral hemorrhage associated with a streptococcal pneumonia.

Acute lesions were absent in 77. Six cases were clinically hypertensive cardiacs. Necropsy revealed marked hypertrophy and severe coronary sclerosis in 4, cerebral thrombosis in 1, and extensive pulmonary infarcts in 1.

The pathologic findings of the other organs in the remaining cases was strikingly different in most respects from the group with the pulse-temperature disproportion. Cerebral lesions comprised the largest group, 18 in number, and included hemorrhages, thromboses, primary and secondary tumors, abscesses, and 1 case of skull fracture. Malignant tumors ranked second with 16. Although many were of abdominal organs, only 1 caused intestinal obstruction.

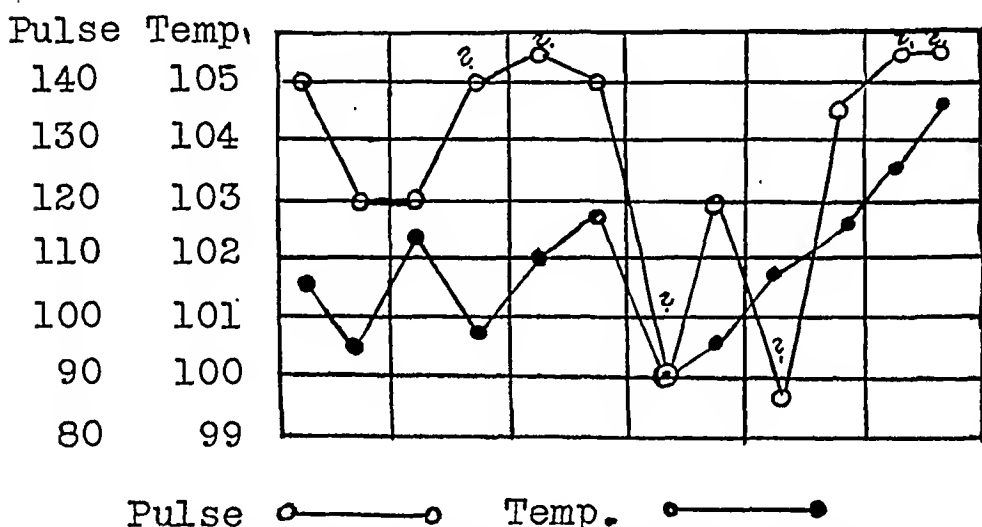


FIG. 3.—Case of chronic active rheumatic heart disease, acute endocarditis, septicopyemia, acute emboli of myocardial branches of coronary arteries and acute miliary infarctions.

The other conditions were acute pneumonia, 12; pulmonary tuberculosis, 6; acute peritonitis, 4; pulmonary embolism, 3; pemphigus, 3; hepatic cirrhosis, 2; and 1 each of cholecystitis, mesenteric thrombosis, decubital ulcers, chronic pelvic abscess, Landry's paralysis, pernicious anemia and glomerulitis.

Tachycardia in pulmonary tuberculosis is frequent. Boas¹ found that it occurred early and was often seen in the later stages. He believed it was a functional manifestation. He quoted Sewall and Head as explaining the tachycardia on a basis of a labile vasomotor system. In the present series, 10 cases showed the pulse-temperature discrepancy; it was absent in 7. Acute myocardial lesions were found in 5 of the first and 1 of the second group.

In intestinal obstruction tachycardia is known to be of almost constant occurrence. The explanation advanced by Ravdin and Abbott³ is that the increased cardiac rate is a compensatory mechanism. They believe that the increased intra-abdominal pressure on the great veins interferes with the return flow of blood to the

heart and that the heart therefore reacts by an increased rate. Six cases of the present series showed the phenomenon, of which 2 had acute myocardial lesions. Only 1 instance of obstruction was present in the group without the phenomenon.

Ravdin's explanation may also be applied to extensive venous thromboses of the inferior cava and its tributaries and to hepatic cirrhosis. In both conditions there is great interference with the

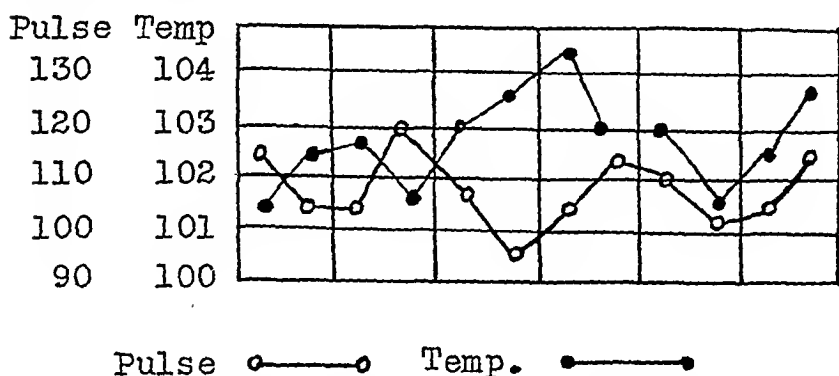


FIG. 4.—Case of hypertension with massive cerebral hemorrhage.

return flow of blood to the heart. There were only 2 cases of venous thromboses, both with discrepancy, 1 with an acute myocardial lesion. Four cases of cirrhosis displayed the discrepancy, 2 did not. An acute rheumatic myocarditis was present in 1 of the 4. Lesions were absent in all the others.

Brain lesions usually have a bradycardia.⁶ Of the 22 cases with cerebral disease, only 1 had a disproportionally rapid pulse and myocardial damage was absent. Twenty-one had either a proportionate pulse or a bradycardia. There were 2 with cardiac lesions, acute miliary infarcts in 1, abscesses in the other.

Summary and Conclusions. In cases with persistent tachycardia and disproportion between the pulse rate and temperature level the acute myocardial lesions were studied. In 100 cases presenting the phenomenon, acute lesions were present in 80, a chronic granulomatous lesion in 1. In 98 cases in which the phenomenon was absent, acute lesions were present in 19, a chronic granulomatous lesion in 1 and amyloidosis in 1. The relation between the pulse and the temperature appears to offer a simple and valuable index to the presence or absence of acute myocardial damage in a high per cent of cases.

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FREQUENCY OF BILATERAL RENAL DISEASE IN PERSISTENT HYPERTENSION.

BY JOSEPH R. KAHN, M.D.,

SENIOR INSTRUCTOR IN EXPERIMENTAL PATHOLOGY, WESTERN RESERVE UNIVERSITY,
AND

THOMAS C. LAIPPLY, M.D.,

CHIEF RESIDENT IN PATHOLOGY, UNIVERSITY HOSPITALS AND INSTITUTE OF PATHOLOGY,
WESTERN RESERVE UNIVERSITY,
CLEVELAND, OHIO.

(From the Institute of Pathology, Western Reserve University and The University Hospitals of Cleveland.)

EXPERIMENTALLY produced unilateral renal ischemia causes hypertension in dogs⁹ and monkeys.^{7a} The elevation of blood pressure does not persist indefinitely unless the other kidney is removed or unless the main artery of the other kidney is also constricted. The elevation of blood pressure produced by constriction of one renal artery in some rats,²³ goats and sheep^{8b} lasts for months without removal of the opposite kidney or constriction of its artery. The constriction of the main artery of only one kidney in animals produces no elevation of blood pressure if its ureter is ligated.^{8a} Unilateral renal disease in man may also result in a hypertension, which is persistent and may reach very high levels. There may be ocular changes with hemorrhage, exudation, edema, retinal detachment and blindness. With the removal of the ischemic kidney, both in animals⁹ and in man,^{1-6,10-15,17-22} the blood pressure will return to its original level if the remaining kidney is normal. Tests of renal excretory function in experimentally produced renal ischemia or in arterial and arteriolar nephrosclerosis may be normal if the ischemia is of moderate degree. Before surgical removal of a diseased kidney, thought to be the cause of hypertension, all types of excretory renal function tests should be performed and intravenous as well as retrograde pyelograms should be made on the opposite kidney as well, in order to rule out any contralateral renal disease. It should be noted, however, that even when all renal function tests and pyelograms are normal, the kidney may still be the seat of vascular disease. It is important, therefore, in studying hypertension in human beings to determine in what proportion the hypertension may be due to unilateral renal disease.

In 1000 patients* who died of conditions directly related to hypertension, and upon whom autopsies were performed, all had a final anatomic diagnosis of arterial nephrosclerosis, arteriolar nephrosclerosis or a combination of the two. Patients with pyelonephritis, congenital polycystic renal disease and nephritis were excluded from

* At University Hospitals of Cleveland, Cleveland City, and Cincinnati General Hospitals.

this series. In all of these patients the renal vascular disease was bilateral. In many instances the degree of vascular involvement was not the same in both kidneys. In 20 (2%) of the patients the two kidneys differed greatly in weight, one being much reduced in weight while the other weighed as much or more than normal. In some the smaller kidney weighed less than 50 gm. Microscopic examination of these small kidneys showed few normal glomeruli or tubules. It may be presumed, therefore, that their function must have been greatly reduced although in none of these 20 patients was there an elevation of nitrogenous products in the blood. Some, to be sure, may have been congenitally hypoplastic kidneys. The larger kidneys must have had a normal or nearly normal function. However, when the large kidneys were examined microscopically, in all 20 cases they were found to be the seat of arterial and arteriolar nephrosclerosis. Thus, in any of these patients, if the smaller and nearly functionless kidney had been removed the blood pressure would probably not have returned to normal.

When hypertension is due to renal vascular disease, not related to pyelonephritis, both kidneys are usually involved. In such individuals the removal of one kidney, even though clinically functionless or nearly so, while the opposite one is functionally normal, will not relieve the hypertension. It is impossible to state that the vascular disease began simultaneously in both kidneys. It may at first have been confined to the smaller one and subsequently, after the hypertension had existed for a period of time, developed in the larger kidney. But, at present, there is no method by which the possible existence of vascular disease in any kidney can be excluded.

Autopsies on 50 cases of chronic pyelonephritis were also studied. Only 10 of these patients showed no renal vascular disease and they did not have hypertension. In 4 instances the pyelonephritis was confined to one kidney but 3 of these nevertheless had bilateral renal vascular disease. In the fourth case the vascular disease was confined to the kidney the seat of chronic pyelonephritis and hypertension was present. However, in the last case the pyelonephritis was secondary to ureteral obstruction by a carcinoma of the bladder, and the patient died of generalized carcinomatosis. In 23 of the 36 remaining patients hypertension was present during their last hospital admission. The remaining 13 did not have hypertension on admission to the hospital but many of them were in shock due to various other conditions. From the weights of the hearts it cannot be stated that they had hypertension.

An analysis was made of the kidney weights of 456 autopsied patients with hypertension, having an anatomic diagnosis of arterial and arteriolar nephrosclerosis. These weights were compared with those of normal kidneys from patients who died without renal disease (see Tables 1 to 4). The tables* show that, on the average,

* There is a difference in the number of right and left kidneys in the tables because some of them were injected for special studies and not weighed.

patients with arterial and arteriolar nephrosclerosis have smaller kidneys, but the difference is not as great as might be expected. In fact, the weight deviation in both the normal and diseased kidneys is so great that there is a considerable overlapping. Many of the kidneys with vascular disease have normal or above normal weights.

TABLE 1.—WEIGHTS OF NORMAL KIDNEYS IN MALES.

Age group.	Right kidney.			Left kidney.		
	No.	Average weight.	S.D.	No.	Average weight.	S.D.
15-24	13	172	±33	13	166	±32
25-34	40	170	±31	40	172	±35
35-44	60	183	±32	62	184	±37
45-54	95	172	±33	96	177	±34
55-64	52	160	±24	54	163	±24
65-74	12	172	±31	13	175	±35
Total	272	171	±32	278	174	±34

TABLE 2.—WEIGHTS OF NORMAL KIDNEYS IN FEMALES.

Age group.	Right kidney.			Left kidney.		
	No.	Average weight.	S.D.	No.	Average weight.	S.D.
15-24	8	153	±40	9	154	±38
25-34	30	154	±32	30	158	±36
35-44	25	174	±32	26	172	±37
45-54	23	164	±27	24	164	±32
55-64	19	146	±25	18	139	±28
65-74	8	132	±24	9	132	±34
75-	2	140		2	133	
Total	116	157	±32	117	157	±37

TABLE 3.—WEIGHTS OF KIDNEYS IN MALES WITH RENAL ARTERIOSCLEROSIS.

Age group.	Right kidney.			Left kidney.		
	No.	Average weight.	S.D.	No.	Average weight.	S.D.
25-34	5	145	±16	4	152	±24
35-44	30	169	±41	29	169	±40
45-54	75	156	±43	73	158	±40
55-64	81	155	±43	80	157	±43
65-74	80	157	±43	81	165	±45
75-84	20	136	±47	20	139	±44
Total	291	156	±43	287	160	±43

TABLE 4.—WEIGHTS OF KIDNEYS IN FEMALES WITH RENAL ARTERIOSCLEROSIS.

Age group.	Right kidney.			Left kidney.		
	No.	Average weight.	S.D.	No.	Average weight.	S.D.
24	1	150		1	100	
25-34	1	100		2	120	
35-44	26	141	±38	26	134	±50
45-54	36	137	±47	36	139	±44
55-64	20	144	±30	19	152	±34
65-74	13	148	±23	15	149	±23
75-	1	85		1	70	
Total	98	140	±39	100	140	±42

By microscopic examination it was found that the kidneys of normal size have arteriolar disease with slight if any involvement of the larger arteries. In some kidneys of normal weight the capsules strip with ease, the external surfaces are smooth and all gross features are those of normal kidneys. Microscopically, these showed marked hyalinizing arteriolar sclerosis, especially of the preglomerular arterioles. That such large kidneys are the seat of ischemia, it is of course impossible to judge on anatomic grounds alone. It is generally thought that renal ischemia, with its associated hemodynamic disturbance, presumably resulting in deficient irrigation of the kidney with blood, initiates the hypertension. Recently Page¹² has suggested that the hemodynamic disturbance consists not so much of a reduction of the blood flow through the kidney as of a reduction of pulse pressure within the kidney. Since, in most of the kidneys, especially those that are of normal weight, the vascular disease is practically limited to the preglomerular arterioles, it is difficult to see how reduction of pulse pressure can occur beyond this site when there is no actual pulsation in the portion of the vascular tree distal to this site. Presumably, glomeruli are composed of capillaries and the tubules are supplied by capillary vessels in both of which pulsation does not occur.

Arteriolar disease of the kidneys alone will not induce marked atrophy of the organ. The reduction in size of the kidneys, in vascular disease, is due mainly to arteriosclerosis of the larger intrarenal arteries or sclerosis with stenosis of the main renal arteries. The weights of the kidneys with arteriolar and severe arterial sclerosis on analysis (Table 5) are found to be significantly smaller than those with arteriolar disease and minimum or only moderate arterial sclerosis.

TABLE 5.—WEIGHTS OF KIDNEYS OF PATIENTS WITH MARKED ARTERIOSCLEROSIS AND ARTERIOLAR SCLEROSIS.

	Right kidney.		Left kidney.	
	No.	Average weight.	No.	Average weight.
Male	52	117 ± 31	47	126 ± 36
Female	54	104 ± 32	48	100 ± 36

The average weight of the kidneys of the uremic patients (Table 6) is less than of those dying of other complications of hypertension. These very small kidneys have not only arteriolar disease but also severe arterial sclerosis. However, in the individual instances the kidneys may weigh even more than normal. This can be expected when it is known that the glomerular counts on kidneys need not closely correspond with the weight of the kidneys.¹⁶

The onset of hypertension is so insidious that the history of the duration of the disease is unreliable. It is, therefore, impossible to determine either by gross or microscopic examination of the kidneys how long any patient may have had hypertension.

Sixty-five (14%) of the 456 patients whose kidney weights were analyzed died of uremia. Some of these were complicated by heart failure, so that it was impossible to tell whether or not the renal disease alone was sufficient to cause the uremia. Eighteen (27.7%) of the 65 uremic patients had necrotizing arteriolitis (malignant hypertension). Arteriolar necrosis was found only in the patients dying with renal insufficiency, although many of the patients whose death was due to cerebral hemorrhage had higher blood pressure. In all of the kidneys showing necrosis of arterioles, chronic vascular disease was very marked. This suggests at least the possibility that renal failure was present and that the arteriolar necrosis was superimposed upon already failing kidneys. This is in agreement with experimental work in which similar necrotizing lesions were observed in animals with hypertension and renal insufficiency.^{7b}

TABLE 6.—WEIGHTS OF KIDNEYS OF PATIENTS WITH UREMIA DUE TO ARTERIO- AND ARTERIOLAR NEPHROSCLEROSIS.

	Right kidney.		Left kidney.	
	No.	Average weight.	No.	Average weight.
Male	37	117	35	118
Female	28	97	25	88

Many of the younger patients who died of hypertension had arteriosclerosis which was confined to the kidneys; careful search disclosed none elsewhere in the body. Thus it is concluded that generalized arteriosclerosis in man is not a necessary accompaniment of hypertension. Furthermore this study offers no support for the view that systemic hypertension causes a generalized vascular sclerosis. There was no pathologic state in these cases to account for the high blood pressure other than the intrarenal vascular sclerosis.

Conclusion. From this study it is obvious that in nearly all cases of persistent hypertension with vascular disease the renal disease is bilateral. The renal involvement may be much more marked in one kidney than the other, and can be so extreme as to produce a functionless or almost functionless organ. All known clinical tests of excretory function may fail to detect renal vascular disease. The weight and size of the kidney are not directly proportional to the degree or duration of the hypertension.

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A RENAL CONCENTRATION TEST EMPLOYING POSTERIOR PITUITARY EXTRACT.

BY WILLIAM A. SODEMAN, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE, TULANE UNIVERSITY; VISITING PHYSICIAN,
CHARITY HOSPITAL,

AND

HUGO T. ENGELHARDT, M.D.,

INSTRUCTOR IN MEDICINE, TULANE UNIVERSITY; ASSISTANT VISITING PHYSICIAN,
CHARITY HOSPITAL,
NEW ORLEANS, LA.

(From the Departments of Preventive Medicine and Medicine, Tulane University.)

THE most satisfactory tests for renal function in many instances are those measuring the concentrating capacity of the tubules. These tests employ a period of water restriction, or deprivation varying from 12 hours to 3 days. The use of posterior pituitary extract about to be described produces a satisfactory test yet eliminates these long periods of fluid restriction or water deprivation.^{3,5}

It was evaluated by submitting patients to three or more of the following five procedures: 1, a modified Fishberg concentration test with restriction of fluids from 6 o'clock the previous evening. The overnight urine was discarded and half-hourly specimens collected from 9 o'clock in the morning until 11 or 12 noon. 2, the same procedure with the administration of 0.5 cc. (10 units) of surgical pituitrin subcutaneously at 9 o'clock in the morning. 3, free access to fluids until 9 in the morning, when they were restricted; the pituitrin administered and 30-minute specimens taken as above. 4, free access to fluids until 9 in the morning, when in 15 minutes, 1600 cc. of water were given followed by administration

of 0.5 cc. of surgical pituitrin either (a) before or (b) after diuresis had started; specimens of urine were again collected at half-hourly intervals. 5, the fourth procedure was repeated without the administration of the pituitrin. Specific gravities were obtained by weighing the urine in a 2-cc. weighing bottle or pyknometer to 0.1 mg. and comparison made with a similar quantity of distilled water at the same temperature according to the usual technique.* Corrections were made for albumin when present.

On 35 individuals, including 20 normal subjects and 15 patients with various degrees of renal impairment, 104 tests have been carried out. Consistent results have been obtained in all. Chart 1 shows the results in 1 subject. The curves are numbered to correspond to the procedures described above. In this instance, the

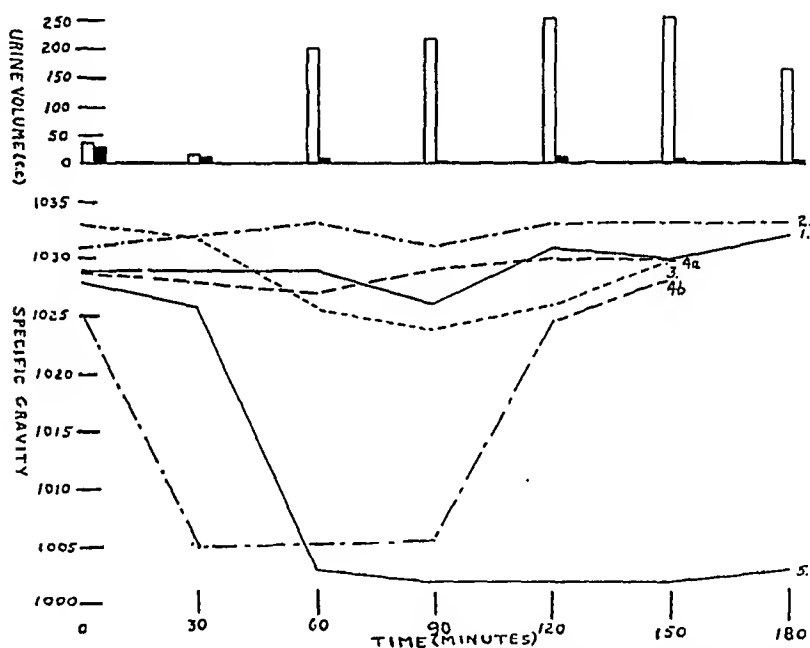


CHART 1.—Results in 1 subject. The curves are numbered to correspond to the procedures described in the text. Black and white columns represent urinary volume corresponding to curves 4a (1600 cc. water with pituitrin) and 5 (1600 cc. water without pituitrin) respectively.

test was carried out in very hot weather, which accounts for the fact that with or without preparation, the urinary specific gravity started in each experiment in a range (1.025) indicative of satisfactory renal function. This fortunate circumstance revealed data which indicated that when water diuresis was inhibited by water restriction (Curve 2), or by excessive loss by perspiration or other routes of excretion (Curve 3), and the initial specific gravity was

* Recently we have been using the Saxe Urinopyknometer, which requires only 3 to 4 cc. of urine, and is accurate, rapid and simple. We are now attempting to establish standards for 2 one-hourly collections of urine to obtain volumes suitable for the ordinary urinometer.

high, the addition of the pituitary extract had little effect in elevating the specific gravity. This is also shown in Chart 2. However, when the specific gravity started in a low range it may be seen (Chart 2) that a marked elevation resulted in normal subjects to values (1.024 in all but 1 instance) indicative of adequate tubular function. These values, however, did not approach those obtained when the specific gravity started in a high range. Since pituitary extract inhibits water diuresis, when the latter is already eliminated, little effect is to be expected upon the specific gravity.

The stimulus to water diuresis instituted by the administration of 1600 cc. of water in 15 minutes at the beginning of the procedure

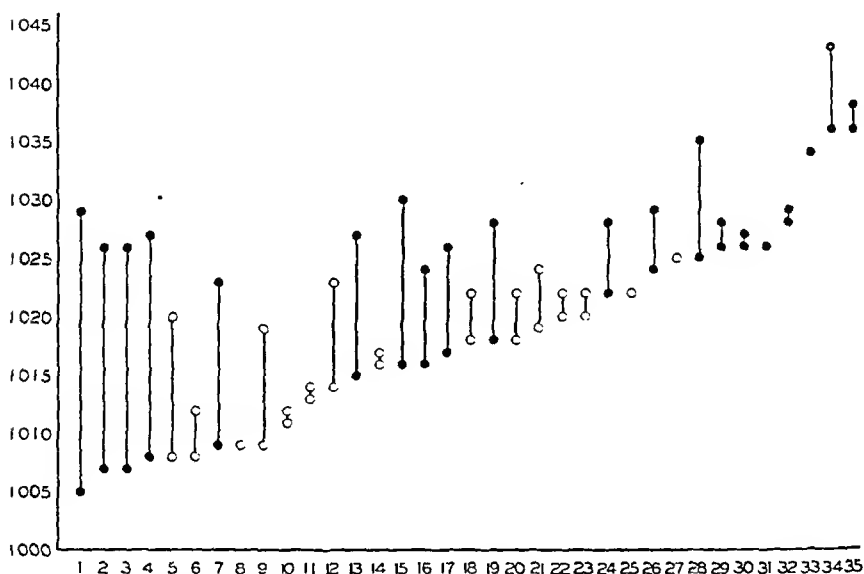


CHART 2.—Results of Procedure 3. The specific gravity before and after the administration of posterior pituitary extract is shown. Black circles represent normal subjects, white circles patients with renal disease as described in text. Ordinates represent specific gravity, abscissae patient number.

(Chart 1, Curve 5) was inhibited by pituitrin whether diuresis had started (Curve 4b) or not (Curve 4a), indicating the effectiveness of this function of pituitrin. This is also reflected in the urinary volumes which, with pituitrin, were maintained at the initial low values (Chart 1). Regardless of preparation of the normal subject, the administration of pituitrin maintained the specific gravities at levels diagnostic of adequate tubular function.

In all normal subjects studied, the results have been similar and in each instance, specific gravity values were equal to or exceeded those obtained by the standard test with water restriction.

Chart 3 shows the results obtained in 2 subjects with slightly and markedly impaired renal function respectively with, 1, the

usual concentration test; 2, the usual concentration test plus pituitrin; and 3, no preparation plus pituitrin. In each instance, the comparative results of each procedure are clearly shown. Further results of Procedure 3 in patients with bilateral renal disease are shown in Chart 2. These patients show varying degrees of impairment of the concentrating ability of the kidneys associated with acute hemorrhagic nephritis (Case 7) and chronic nephritis (Cases 9, 10, 11, 12, 20, 25), including uremia (Cases 6, 8, 14), and arteriosclerotic heart disease (Cases 5, 18, 21, 22, 23).

Patients 18 and 21 represent instances of congestive heart failure in which diuresis of edema fluid was actively progressing at the time the procedure was carried out. In both patients the usual concentration test without pituitrin failed to indicate the concentrating

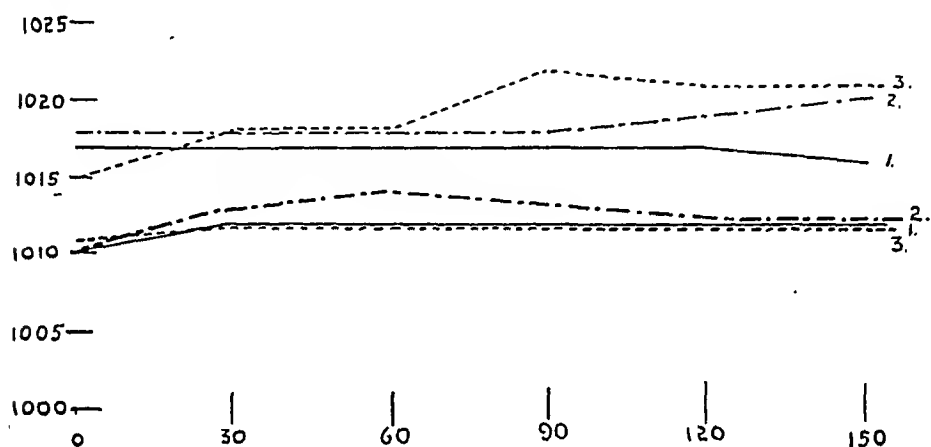


CHART 3.—Results obtained in 2 patients, 1 with slightly impaired renal function (upper 3 curves) and 1 with markedly impaired renal function (lower 3 curves). Ordinates represent specific gravity, abscissae time in minutes for procedures numbered as described in text.

ability of the kidneys because of the diuresis. Values were raised to 1.015 and 1.018 without pituitrin and to 1.022 and 1.024 with pituitrin.

Discussion. Of the procedures described above, that employing pituitrin with no preparation of the patient was found to give entirely suitable results. In health, the urinary volume and specific gravity depend upon the quantity of fluids ingested and the extrarenal fluid loss. When large quantities of fluid are taken, a urine of low specific gravity is produced, while with limited intake, especially if loss through perspiration, diarrhea or other extrarenal routes is great, the urine will be scanty and concentrated. The tests of urinary concentration in use today employ a period of water restriction varying from 12 hours to 3 days to produce a satisfactory inhibition of water diuresis and consequent elevation in the urinary specific gravity. The action of posterior pituitary extracts eliminates the need for these long periods of water deprivation. The

antidiuretic action of posterior pituitary extract results from an increase in the reabsorption of water by the tubules. In this way, the urinary volume is diminished and the specific gravity elevated in the face of water diuresis, which is inhibited. The degree to which the specific gravity is raised would depend upon three or more factors, including the dosage or effectiveness of the pituitrin, relative to the degree of water diuresis present, the tubular function and the electrolyte and non-electrolyte pattern in the urine.

The dosage of pituitrin used has to be kept within a value which is not only safe for clinical use but also is sufficiently effective in the face of even extreme water diuresis to elevate the specific gravity of the urine in normal subjects to values which are considered in other renal concentration tests¹ to be indicative of adequate tubular function. It was pointed out above that although the rise in specific gravity was greater in general, when it started in low rather than in high range, higher final values were obtained with higher initial specific gravities. In other words, the higher the specific gravity in the normal subject when posterior pituitary extract is administered, the higher in general will be the resultant specific gravity. If the specific gravity starts in a high range and water is administered followed immediately by pituitrin, higher values may be maintained than those obtained (Curve 4b) if diuresis is started with 1600 cc. of water and the specific gravity reduced before the pituitrin is administered to elevate it. Even though pituitrin will elevate the specific gravity to satisfactory diagnostic levels after water diuresis with large volumes of water has started, it will not elevate the specific gravity in all instances to values which may be obtained by long periods of water restriction or extrarenal loss. In Chart 1, for example, a specific gravity of 1.031 was obtained with the latter procedure, while after water diuresis, permitted to go until a low specific gravity was obtained, pituitrin in the dosage used elevated the specific gravity to only 1.028. The latter figure, however, is considered to indicate a normal tubular function.

That the specific gravities obtained after pituitrin are not "ceiling" values may be due to a number of factors. Increased dosage of pituitrin might be more effective in certain instances but in several subjects, in whom the dose was doubled, no significant increase was found. The electrolyte-non-electrolyte pattern and the variable concentration of these substances in the urine may be in part responsible in that salt diuresis may be instituted with a varying concentration of the substances which make up the specific gravity of the urine. We have thus far not studied these effects and therefore cannot evaluate them. Whether or not there may be a limit to the ability of the tubules to reabsorb water above which an excess would result in water diuresis which could not be controlled by

pituitrin, we do not know. If this is true, this factor may come into play. However, even under these circumstances the ingestion of 1600 cc. of water in 15 minutes is not sufficient to drop the specific gravity with pituitrin below values of use in diagnosis. These results confirm the observations of Pasqualini and Etala,⁴ who found in 40 normal subjects that the diuresis produced by the ingestion of a liter of water was inhibited by pitressin. In 18 of their subjects in whom the specific gravity started in a low range the values were elevated in the face of the ingestion of a liter of water to 1.025 or more. In our group, the lowest value obtained was 1.024, except in 1 instance where the specific gravity reached 1.023. This patient was a man of 35 convalescing from pneumococcic pneumonia without any evidence of renal disease.

It is to be emphasized that, in the same normal subject, concentration tests now in use give various values for specific gravity depending upon the degree of water restriction. In normal subjects higher values are obtained at times by prolonged periods of water restriction than with posterior pituitary extract. Under similar conditions with periods of water restriction up to 16 to 18 hours this has not been the case. It is obvious that the procedure does not give "ceiling" specific gravity but that the standards set up for normal subjects are workable ones.

The highest specific gravities were obtained, following pituitrin, in a period varying from 1 to 2 hours. Similar time intervals for maximum specific gravities were obtained by Pasqualini and Etala even after the ingestion of a liter of water. When the bladder is emptied at the beginning of the test, a specific gravity determination on that specimen may be obtained immediately and the test discontinued before the pituitrin is given if the value obtained is sufficiently high to indicate adequate tubular function.

Impairment of renal tubular function is characterized by impaired concentrating ability. When such a patient is deprived of water or when the extrarenal loss of water is excessive the degree of urinary concentration, as reflected in the specific gravity, is impaired depending upon tubular function and the amount of water restriction. As tubular function becomes impaired and the concentrating ability of the kidney reduced, there is a striking parallelism in results of the tests employing water restriction and that employing pituitrin (Chart 3). The results in 15 patients with renal disease shown in Chart 2 demonstrate the applicability of the procedure to such patients. Patient 27 with acute hemorrhagic nephritis showed specific gravities well within normal range. With markedly impaired renal function with uremia (Patients 6 and 8), markedly impaired concentrating ability is shown. In both the normal and abnormal group the dosages of posterior pituitary extract used have produced no significant changes in the blood pressure, even in the presence of

marked hypertension and uremia. We have not used the procedure in patients with marked oliguria, pregnancy, angina pectoris, or myocardial infarction. Posterior pituitary extract in patients with angina pectoris has been known to precipitate attacks. However, in arteriosclerotic heart disease with congestive heart failure, we have used posterior pituitary extract without the observance of any untoward symptoms. Graybiel and Glendy² have found no significant cardiovascular symptoms in patients with arteriosclerotic heart disease with angina, after slow intravenous infusion of a dilute solution of pitressin in doses adequate to produce pallor and uncomfortable abdominal cramps.

In the presence of congestive heart failure with diuresis active from treatment the use of concentration tests is unsatisfactory because of the water diuresis from edema fluid and the inability to obtain adequate specific gravity determinations. In several instances of this type described above posterior pituitary extract produced inhibitions of water diuresis sufficient to obtain an estimation of tubular function. Posterior pituitary extract produces its major pharmacodynamic effect for periods of 3 to 6 hours after which diuresis is again resumed.

The procedure described has certain advantages in clinical practice. The test may be carried out on unprepared patients at any time of day. This is advantageous in office practice, especially where patients may come some distance for consultation and may be seen only once. Likewise, in surgical patients, or in others in whom it is not desirable to wait the time necessary for concentration by water deprivation or to withhold fluids, the test is particularly applicable. The same is true under circumstances where coöperation of the patient is not satisfactory in the control of water intake.

Summary and Conclusions. A procedure employing posterior pituitary extract is described for determination of renal tubular function. It differs from the usual concentration tests in that a period of water restriction or deprivation is not necessary. Unprepared patients, after voiding, are given 0.5 cc. posterior pituitary extract (10 units) subcutaneously and specimens collected at half-hourly intervals for 4 specimens (2 hours). Specific gravities determined in the pyknometer or with the Saxe urinopyknometer, which uses only 4 cc. of urine, may be used as an index of renal tubular function. Advantages and contraindications to the test have been pointed out.

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A PRELIMINARY REPORT ON THE TREATMENT OF AGRANULOCYTOSIS WITH SULFATHIAZOLE.

BY WILLIAM DAMESHEK, M.D.,

AND

LOUIS E. WOLFSON, M.D.,

BOSTON, MASS.

(From the Beth Israel Hospital.)

DESPITE the claims made for the pentose nucleotides, adenine sulphate, liver extract, transfusions, yellow bone-marrow extract, and so on, the treatment of agranulocytosis has failed to change the essentially fatal outcome of the disease. Death is probably the result of overwhelming sepsis in a body stripped of its granulocyte defenses. To combat the sepsis might be of definite value. With this thought in mind, sulfathiazole in large dosage was given in addition to transfusions and pentnucleotides in our last 2 cases. Although no proof is present that the sulfonamide drug was curative, it did no harm, and we believe it may have been of value in combating the secondary sepsis. Further trials in other cases of agranulocytosis are indicated. Of theoretical interest is the fact that the sulfonamide drugs may have their characteristic action in the absence of granulocytes.

Case Reports. CASE 1.—Harold P., a 40-year-old, single, office worker, was admitted to this hospital (No. 55070) on October 13, 1940, delirious and irrational after a week's illness with fever, headache, and severe sore throat. Aminopyrine had been used 3 years previously and just prior to the onset of the present illness. The patient was semi-moribund, irrational, and having great difficulty in breathing. The temperature was 104° F. (rectal), pulse 144 per minute, respirations 35. The buccal mucous membranes, gums, tongue, and throat showed the characteristic necrotic lesions of agranulocytosis and there was marked swelling at the angles of both jaws. The abdomen was greatly distended with gas. Over the skin of the trunk were present many dark red necrotic papules.

The blood showed hemoglobin 80%, white blood cells 750 per c.mm., with complete absence of granulocytes. All the leukocytes were small lymphocytes. The blood platelets were abundant.

Pentnucleotides were immediately begun in dosage of 10 cc. intramuscularly four times daily, and on the following day (10/14) a transfusion of 500 cc. of blood was given from a compatible donor. The patient was now completely irrational, incontinent and semicomatose. The temperature had risen to 105° F., the pulse rate was 130 per minute, and the respirations varied between 20 to 28 per minute. The leukocyte count was 850 per c.mm. with complete lack of granulocytes. The outlook seemed almost hopeless. Because of the definite likelihood that the fever and prostration were due to bacterial invasion of the blood stream in an individual depleted of granulocytes, and because it was felt that death in agranulocytosis is due, not to the lack of granulocytes, but to bacteremia, it was decided to try to sterilize the blood stream by the use of one of the sulfonamide preparations. Sulfathiazole was selected because of its known potency against a variety

of organisms. The first dose (2 gm.) of this drug was therefore given at midnight, October 14, and followed by 1 gm. doses six times daily. Pentnucleotide in 10 cc. doses every 6 hours was continued, together with daily transfusions of 500 cc. of blood on October 15 and 16.

On October 15, the patient's condition was unchanged, but on the morning of October 16 he seemed slightly improved. A sternal puncture showed almost complete absence of granulocytes, most of the leukocytes present being large lymphocytes and plasma cells. At 4 p.m. (40 hours after beginning treatment with sulfathiazole) the white count was 1400 per c.mm. and 4 granulocytes (all of them either young or "band-form" metamyelocytes) were found!

TABLE 1.—HEMATOLOGIC DATA IN CASE 1.

Date 1940.	Hgb. (%).	R.B.C. (mill.).	W.B.C.	Neutrophils.		Lympho- cytes.	Mono- cytes.	Remarks.
				Total (%).	Imma- ture (%).			
10/13	80	..	750	0	..	100	..	Pentnucleotide 40 cc. i.m. daily.
10/14	79	4.12	850	0	Transfusion 500 cc.; sulfathiazole begun at midnight—6 gm. daily.
10/15	950	0	..	100 (2 plasma cells)	..	Transfusion 500 cc.
10/16 A.M.	95	4.90	700	0	Transfusion 500 cc.
10/16 P.M.	1,400	4	3	96	..	Sternal puncture.
10/17 A.M.	89	4.48	1,150	14	12	86	..	Patient improved.
10/17 P.M.	2,250	26	21	74	..	Occasional myelocyte.
10/18	3,150	46 (5 myelocytes)	40	48	1	Sulfathiazole omitted.
10/19	5,650	69 (5 myelocytes)	38	26	..	Cough.
10/20	13,100	74	33	24	2	Resolving lobar pneu- monia discovered.
10/21	13,300	65	24	32	3	
10/22	12,050	75	24	23	2	Slight fever; marked tachycardia.
10/24	11,900	68	9	25	7	
10/31	89	4.62	10,000	83	11	11	6	Sulfathiazole 6 gm. daily.
11/2	9,100					
11/6	9,500					
11/14	92	4.72	8,700	65	3	21	14	Sulfathiazole omitted 11/12.

On October 17, the patient was definitely better, and from then on there was continued improvement despite the development of bilateral pulmonary consolidation. This had apparently been present during the period of complete agranulocytosis but had not been recognized until the patient's cough and general condition on October 20 warranted examination of the chest. On October 30, sulfathiazole was again given when there was a flare-up in the pneumonic consolidation. The patient made a complete and uneventful recovery.

CASE 2.—Mrs. Ina S., an 80-year-old retired housewife, was seen by one of us (W. D.) with Dr. W. E. Greer at the Alexander Eastman Hospital of Derry, N. H., on May 22, 1941. On May 17, she took 2 tablets (0.6 gm.) of aminopyrine for one of her occasional severe headaches for which she had previously taken the same drug. On May 19, she complained of a sore throat. On May 21, because of the development of severe constitutional symptoms, notably fever, prostration, and drowsiness, the patient was admitted to the hospital, where she rapidly became worse. Routine blood counts revealed the following: hemoglobin, 88%; R.B.C., 4.49 million; W.B.C., 500 (!) and complete absence of all leukocytes but the lymphocytes. Intravenous fluids and pentnucleotide, 1 ampoule every 6 hours, were given but the patient rapidly became more stuporous and vomited frequently.

In quick succession, delirium, abdominal distention, tracheal râles, and a feeble, irregular pulse developed.

On the morning of May 22, the patient was semimoribund and slightly jaundiced. The temperature was 104.5° F., the pulse 120, and the respirations 30 per minute. The mouth and throat showed the typical dry, necrotic lesions of agranulocytosis. The neck was slightly swollen especially at the right. The heart revealed rather distant sounds with numerous extrasystoles. The abdomen showed moderate distention. The liver was felt 2 finger-breadths below the right costal margin.

TABLE 2.—HEMATOLOGIC DATA IN CASE 2.

Date 1941.	Hgb. (%).	R.B.C. (mill.).	W.B.C.	Neutrophils.		Lympho- cytes.	Mono- cytes.	Remarks.
				Total (%).	Imma- ture (%).			
5/21								
A.M.	88	4.49	500	0	..	100	..	Sulfathiazole 12 gm. 5/19-5/21.
P.M.	325	0	..	100	..	Pentnucleotide 1 am- poule q. 6 hrs.; liver extract 45 units i.m. q. 4 hrs.
5/22								
A.M.	500	0	..	99	1	Temp. 104.5° F.
P.M.	750	0	..	100	..	Sulfathiazole 1 gm. q. 4 hrs.
5/23	1,000	0	..	100	..	Sulfathiazole 7 gm. given 5/22-5/23.
5/24	2,700	5	5	83	12	Patient impr.; temp. 101.5° F.; sulfa- thiazole discont.
5/25	8,400	Temp. 100.5° F.
5/26	14,400	61	31	34	5	Pentnucleotide 1 am- poule q. 8 hrs.; liver extract 30 units q. 6 hrs.
5/27	16,500	66	24	30	4	Pentnucleotide 1 am- poule twice daily; liver extract 30 units twice daily.
5/28	17,500	62	23	36	2	
5/29	17,900	82	31	17	1	Pentnucleotide and liver extract discon.
5/30	18,000	70	31	27	3	Progr. improvement.
5/31	18,500	69	24	27	4	
6/2	96	4.89	12,000	68	9	30	2	
6/4	9,500	68	5	29	3	
6/9	88	4.48	7,500	67	3	31	2	

A staphylococcus in pure culture was isolated from the throat. The urine showed a large trace of albumin and contained bile. The leukocyte count was 500 per c.mm. with 99% lymphocytes and 1% monocytes. Because of our experience in Case 1, it was recommended that sulfathiazole be given. This recommendation was accepted by Dr. Greer and after the first dose of 2 gm., the patient was given the drug in dosage of 1 gm. at 4-hourly intervals. In addition, the pentose nucleotides were still continued in dosage of 1 ampoule intramuscularly every 6 hours; liver extract injections (45 units) were given intramuscularly every 3 or 4 hours, together with intravenous fluids, subcutaneous prostigmin to combat the distention and coramine.

On May 23, approximately 18 hours after administration of the drug was begun, the patient stated that she felt better and appeared brighter and stronger. The temperature had dropped to 101.4°, the pulse to 100 per minute. The leukocyte count was 1000 per c.mm., all the cells being lymphocytes. The drug was discontinued after another dose was given. On the following day, the white cells numbered 2700 (!), and of 100 leukocytes 5 were immature granulocytes with 83 lymphocytes and 12 monocytes. The course from then on was one of continued improvement, both clinically and hematologically.

Comment. The development of agranulocytosis following the use of drugs, particularly aminopyrine, is too well known to warrant further comment. Due to the lack of neutrophils, the normal bacterial flora of the mouth, throat, and other cavities flourish in unusual abundance with resultant sore throat, lesions of the buccal and other mucous membranes. In the absence of neutrophils and their normal defensive mechanisms, sepsis due to blood stream invasion ensues. Death is probably due not to the lack of neutrophils *per se* but to the resultant sepsis. From the blood stream of patients dying of the disease numerous virulent organisms have been isolated. Formerly considered to be the cause of the condition, their true nature as secondary invaders has become firmly established. The use of sulfathiazole in the cases here presented was based on these reasons. It was believed that if the invading organisms could be "held in check" by the drug while natural processes in the bone marrow concerned with leukopoiesis might become reestablished, the patient might recover.

Our experience with the pentose nucleotides and their derivatives (adenine sulphate and guanidine hydrochloride) has been extremely disappointing in the past few years. In a series of 12 cases reported in 1936³ there was recovery in 8. In the last 5 years, 30 cases have been seen. Of these, all but 2 died despite very active treatment with pentose nucleotides, adenine sulphate, transfusions, and so on. The recoveries occurred in 2 relatively mild cases in which coma did not develop and the dosage of aminopyrine which had been administered was very small. As a result of these experiences, our former rather optimistic attitude regarding the value of the nucleic acid derivatives has become greatly modified.² The critical situation in agranulocytosis may be said to lie: 1, between the capacity of the marrow to recover, after an extremely hypersensitive reaction; and 2, the rapidity of the development of septicemia. In recent years, the latter question has received but scant attention. However, with the development of the sulfonamide drugs, this question deserves renewed consideration, although the medical profession is somewhat loath to give these drugs in the presence of leukopenia. This attitude has naturally developed because of the occasional cases of agranulocytosis which occur during the course of treatment. However, it is well established⁴ that if leukopenia is due primarily to an infectious process, use of a sulfonamide drug will not only do no harm but will often result in an increase in the leukocyte count and in cure of the disease.

The use of a sulfonamide drug in the presence of complete lack of granulocytes is also of some theoretical interest since it is confirmatory of the thesis that the neutrophil is not essential in the activity of the drug. Although the exact mechanism of the drug's action is as yet not clear, most authorities are in accord that it has a direct action on the bacteria themselves, probably in the nature

of bacteriostasis.^{3,4} The dramatic results in our cases indicate that the drug may be quite as effective in the absence of granulocytes as with large numbers being present.

Because of our experience with the 2 cases presented in this paper, it is suggested that a trial with sulfathiazole or sulfadiazine be made in other cases of agranulocytosis. When the condition is itself due to a sulfonamide drug, one can only hope for either spontaneous recovery of the possible effect of the pentose nucleotides, although in a case of sulfanilamide agranulocytosis, one might consider the use of sulfathiazole or sulfapyridine and *vice versa*.

Summary. Two cases of severe agranulocytosis were treated, in addition to transfusions, pentose nucleotides and liver extract, with large doses of sulfathiazole. The ensuing recoveries may have been due, in part at least, to the effect of the sulfonamide drug on the sepsis which was almost certainly present, thus allowing spontaneous leukocytic regeneration in the bone marrow to take place. Sulfonamide drugs may be effective even in the complete absence of granulocytes.

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ABNORMAL ACCUMULATIONS OF LYMPH FOLLICLES IN THE DIGESTIVE TRACT.

BY PETER GRUENWALD, M.D.,

ASSOCIATE, DEPARTMENT OF ANATOMY, THE CHICAGO MEDICAL SCHOOL,
CHICAGO, ILL.

THE occurrence of large circumscribed masses of lymph follicles in the mucous membranes of the intestinal tract is not mentioned in most of the standard textbooks. In the few reports in the literature (see below), the authors offered various explanations for the genesis of the condition. In the present report, 5 related cases will be described and an attempt will be made to arrive at a satisfactory concept of the nature and development of these abnormal structures.*

Observations. All 5 specimens were obtained at operation. As usual, their peculiar structure was not recognized until histologic examination was done. The common characteristic of all cases is the presence of lymph follicles forming compact masses in locations where they usually do not occur in such large amounts. The

* These cases were collected in the Department of Pathology of Krankenanstalt Rudolfstiftung in Vienna. The author is indebted to Prof. A. Priesel, Director of this department, for leaving him the specimen for description and further supporting the work by valuable suggestions.

follicles themselves have large pale staining centers (so-called "germinal centers") and do not differ from normal ones as far as their minute structure is concerned.

Case Reports. CASE 1.—(627/1929.) "Polyp" of the intestine of a 20-year-old woman. The tissue, nearly 1 cm. in diameter, was covered with mucosa on almost its entire surface, and apparently ulcerated in one place. Histologic examination revealed accumulations of lymph follicles partly covered by intact mucous membrane (Fig. 1). The follicles themselves were occupied to a greater part by irregularly shaped so-called germinal centers, appearing to be confluent. They contained many reticulum cells laden with basophilic debris.* The tissue between the follicles was infiltrated by lymphocytes which were arranged in long lines parallel to the borders of the follicles.



FIG. 1.—Case 1. A protrusion of the mucous membrane of the rectum is caused by lymphoid tissue with numerous so-called germinal centers. (Hemalum—eosin stain.)

CASE 2.—(3003/1930.) "Polyp" of the rectum of a 60-year-old woman. A piece of tissue the size of a bean and another somewhat smaller were submitted for histologic examination. They were almost entirely covered with mucosa. Microscopically, both contained lymphoid tissue in the submucous layer. Many follicles with so-called germinal centers were present; the histologic picture was similar to that of Case 1.

CASE 3.—(1272/1932.) Rectum of a 48-year-old woman. In a piece of rectum 20 cm. long, including the anal ring, there was an area 7 cm. long near the anus with a thickened, uneven mucous membrane. On section the wall appeared thickened and whitish-gray. All layers were apparently infiltrated by abnormal tissue, but still distinguishable. The surrounding

* It should be noted that in this and in subsequent cases the so-called germinal centers show no sign of lymphocytopoiesis, but rather that of reaction by reticulum cells.—ED.

fat tissue contained several lymph nodes up to 7 mm. in diameter, most of them purplish-gray and soft, only a few were whitish-gray and firmer in consistency. Histological sections (Fig. 2) showed that the thickening of the rectal wall was caused by lymphoid tissue. Follicles with well developed so-called germinal centers were found in different layers, increasing in number towards the lumen. The muscle layers were also involved to an extent described never before. The so-called germinal centers were strikingly poor in cells and in many places sharply delimited from the periphery of the follicles by a continuous membrane staining red with eosin. This membrane probably consisted of connective tissue compressed by the growth of the so-called germinal centers.

CASE 4.—(513/1934.) Appendix of a 19-year-old man. The specimen measured 9 cm. in length and 1 cm. in diameter. The peritoneal surface and the thickened inner layers were pale, the lumen was very narrow, and remains of old adhesions could be seen on the serosa. The histologic diagnosis of old appendicitis was made. However, an atypical abundance of

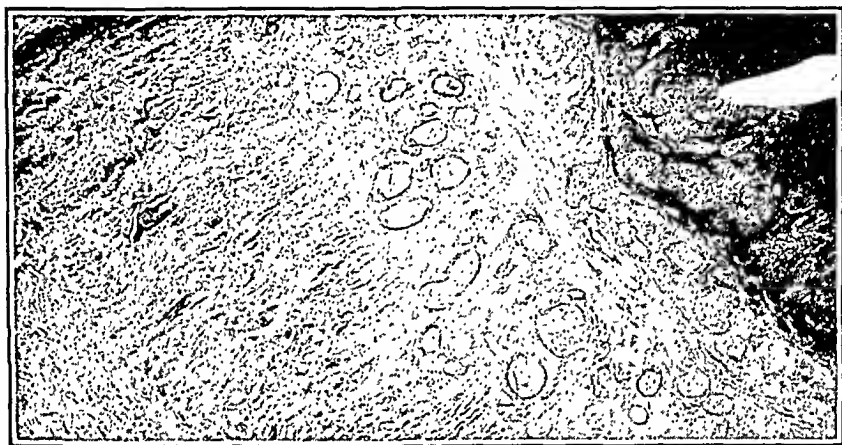


FIG. 2.—Specimen of Case 3. All layers of the wall of the rectum contain lymph nodules, increasing in number towards the lumen (right side of figure). (Hemalum—eosin stain.)

lymph follicles was noticed, even in the peripheral layers, reaching into the fat tissue of the mesentery. The number of nodules decreased towards the periphery. The follicles in the mucosa were occupied almost completely by so-called germinal centers, except that on the side nearest to the lumen, their centers were covered by considerable accumulations of lymphocytes.

CASE 5.—(1557/1936.) Appendix of a 5-year-old girl. A piece of tissue, measuring 5 by 3 by 2 cm. with irregular surface, showed a peritoneal surface covered with pus and fibrin. On the cut surface the appendix itself became visible, embedded in rather firm fat tissue. It was 12 mm. in diameter and its wall was thickened. Near its middle in an area of about 1 cm. all layers of the wall appeared necrotic and impregnated with blood. There was also a small perforation. Histologic diagnosis was made of recurrent appendicitis with severe destruction of the wall and remains of abscesses. In this case, too, an atypical hyperplasia of the lymphoid tissue was present. The follicles formed groups of several millimeters in diameter within the mucous membrane. Between the bundles of the muscular wall there was a considerable infiltration of lymphocytes lying scattered as well as in larger groups.

Comment. Very little mention is made in the literature of the condition described here. The textbooks of Bell,¹ Boyd,^{2a} Delafield and Prudden,⁵ Duval and Schattenberg,⁷ Ewing,⁸ Karsner,¹² MacCallum,¹⁷ and Smith and Gault²⁰ do not describe it; only in his "Surgical Pathology," Boyd^{2b} briefly mentions the occurrence of abnormally large masses of lymph follicles in the appendix. There are, however, indications that the condition in question occurs more frequently than the scanty references would show: The cases described here, as well as those reported by Kengyel,¹³ and Steindl²¹ (see below) were observed in one hospital within a period of a few years.

The present observations as well as those reported in the literature show that the appendix and rectum are the favorite localizations of large accumulations of lymph follicles, although other localizations in the intestine or other organs have also been described. It is not surprising to find the appendix mentioned in this connection because it normally contains large amounts of lymph follicles. This does not hold for the human rectum. Comparative anatomy, however, shows that in this location, too, lymphoid tissue is accumulated in many species of mammals, especially in ruminants (see Patzelt¹⁹). This suggests the hypothesis that the rectum generally has at least a higher disposition to develop lymph follicles to a greater extent. Bartel (cited after Steindl²¹) even suggested the term *tonsil of the rectum* in connection with a pathologic formation similar to our cases.

The origin of the structures in question is not known. Two opinions are represented in the literature. Lehmann¹⁵ and Knoflach¹⁴ regard the polypoid formations of lymphoid tissue which they found in the rectum and appendix as tissue malformations, that is, as congenital anomalies. This opinion is rejected in more recent reports. Nishikawa¹⁸ believes that lymphoid tissue is never found in the peripheral layers of the wall of sound appendices or those with the first attack of acute appendicitis. It may, however, be seen there in cases of subacute inflammation, after repeated acute attacks, or in cases of healing appendicitis. Consequently, Nishikawa supposes some connection with inflammatory processes. Christeller and Mayer,⁴ Kengyel,¹³ and Steindl²¹ hold similar opinions. The development of a lymphoid hyperplasia is regarded by these authors not as a part of the inflammatory process itself, as for instance the formation of a granulation tissue, but as a reaction to a stimulation by the inflammation. The inflammation itself is said to induce the beginning of the hyperplasia which may then proceed, or at least remain stationary, after regression of the inflammation. Nishikawa also believes that the new formation of lymphoid tissue is not part of the inflammation proper, but a secondary process that may continue indefinitely and independent of the course of the inflammation itself. In this connection it is interesting to note that regional ileitis may produce conditions similar to those described

here after regression of the acute inflammation. This is well illustrated by a figure in Smith and Gault's²⁰ textbook.

There is no reason to assume that a specific stimulus has produced the proliferation of the lymphoid tissue in all cases reported until now, a stimulus which would act in the same manner in every human organism. The last-mentioned concept holding that inflammation induces the development of these lymphoid hyperplasias, must, therefore, be supplemented by the assumption of a special disposition of the organism or organ affected. This, then, recalls the idea of a congenital malformation as advanced by the earlier observers. Both theories presume a congenital disposition which, according to the conception of a congenital malformation, leads with certainty to a hyperplasia of the lymphoid tissue, or, according to the modified second theory, becomes effective only in combination with a stimulus as, for instance, an inflammation. The latter concept seems to approach Loeffler's¹⁶ hypothesis that embryonic rests may start growing under the influence of irritations. We now know that the assumption of such remains is unnecessary because the normal tissues have sufficient potencies to account for these formations. However, Loeffler's reference to irritations in general as the stimulus for the growth of the lymphoid tissue is well justified. According to Glimstedt,⁹ who investigated the development of the lymphatic system of guinea-pigs brought up and living under sterile conditions, bacteria or their products are indispensable for the normal growth of the lymphoid tissue. The bacteria living in the normal intestine are thought to bring about this growth without causing inflammation. Consequently, non-inflammatory irritations must be considered as possible stimuli, although the effect of inflammatory processes may be greater. Among inflammations, the effect upon the lymphoid tissue is not limited to bacterial processes. Experiments carried out by Christeller³ and Jacobj¹¹ showed that aseptic inflammation, as produced in the urinary tracts of dogs and cats by sterile foreign bodies or chemicals, is followed by the formation of lymph follicles in the surrounding tissue.

Concluding, we find that apparently hyperplasia of the lymphoid tissue can be stimulated by different kinds of agents, among which bacterial inflammations probably are the most common and effective ones. It is generally accepted that the response to such stimuli is an important physiologic activity of the lymphoid tissue. It is suggested here that in certain cases, presupposing a peculiar disposition, physiologic or pathologic stimuli induce abnormal hyperplasia of the lymphoid tissue, leading to the formation of structures like those described in this report. It must be admitted, however, that congenital hyperplasia developing independent of external factors may produce the same effect. Both these possibilities may well occur; the fact that a formative process may go on independent of external stimuli in some cases, and dependent in others, is not sur-

prising. It is a well-known fact of developmental physiology, confirmed by many embryologic experiments, that transitions between independent and dependent development exist in normal organogenesis, too.

The concept of the origin of certain circumscribed lymphoid hyperplasias, as suggested here, is only a hypothesis. Its correctness can neither be proved nor disproved by case reports as long as we do not know more about the normal and abnormal reaction and growth of the lymphoid tissue.

Not much can be contributed to the clinical aspect of the problem under consideration. The differential diagnosis between lymphoid and ordinary polypoid hyperplasias will probably always remain a matter of histologic examination. Cases with infiltration of all layers of the intestinal wall, such as our Case 3, will probably cause the greatest diagnostic difficulties because malignancy must be ruled out. Dukes,⁶ after describing 3 cases located in the rectum, especially emphasized the possibility of confounding the structures in question with malignant neoplasms. Neither clinically nor histologically is there any evidence of malignancy in the formations described here. In the appendix, Gray and Heifetz¹⁰ pointed out that lymphoid hyperplasia can be of great importance because it may simulate or even produce appendicitis. As stated earlier in this report, benign hyperplasias of the lymphoid tissue, as described here, seem to occur more frequently than is usually believed.

Summary. Five cases of circumscribed hyperplasia of histologically normal lymphoid tissue in the intestinal tract are described. It is suggested that the formation of these structures requires a certain disposition and also a stimulation of the tissue involved. The importance of either of these factors may vary in individual cases.

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THE DIAGNOSIS OF MULTIPLE MYELOMA BY STERNAL ASPIRATION.*

By LAWRENCE H. BEIZER, M.D.,
FELLOW IN MEDICINE, MAYO FOUNDATION,†

BYRON E. HALL, M.D.,

AND

HERBERT Z. GIFFIN, M.D.,
DIVISION OF MEDICINE, MAYO CLINIC,
ROCHESTER, MINN.

THE first adequately described case of multiple myeloma was published in 1850 by Macintyre.⁸ Since then information concerning this disease has slowly accumulated, but, even at the present, our knowledge of its pathogenesis is vague and diagnosis presents many problems. Ewing³ stated that myeloma is used to designate tumors of the specific bone marrow cells; he included the lymphocyte, granular leukocyte and red cell series but excluded tumors arising from fat tissue, blood-vessels and those derived from indifferent endothelial cells. The adjective, multiple, is not strictly accurate since it is known that these tumors may arise in a single focus which may reach a considerable size before multiple tumors appear. Four types of myeloma have been reported: the plasma cell type, the myelocytoma, the lymphocytoma and the erythroblastoma. These differ only in the cytologic composition of the tumor masses and not in the gross appearance of the tumors or in the clinical course.

The identification of the cell-type depended for many years on the appearance of the cells in histologic sections. It is interesting to note that Wright¹⁶ in 1900, from a study of histologic tissue, concluded that "the cells making up the bulk of the tumors are very like or identical with plasma cells" and that Christian¹ in 1907, from a histologic study of 6 cases, described the so-called myeloma cell and noted its resemblance to plasma cells.

Recently, especially since sternal aspiration has been used extensively, the cells have been classified according to their appearance in dry smear preparations stained with stains of the Romanowsky type. Almost invariably tumors studied in this manner have been classified in the plasma cell group.¹² Because of this it has been

* Read before the meeting of the Association of American Physicians, Atlantic City, New Jersey, May 7, 1941.

suggested that only one type of cell is involved in all cases. Whether to call this cell a plasma cell or merely a myeloma cell also has been questioned, since the cells differ in various respects from the classical descriptions. Published criteria for the recognition of typical plasma cells vary from the rather indefinite ones of Cajal and of Unna to the strictly delineated ones of Marschalko which refer particularly to the morphologic appearance of the cells in histologic sections.⁹ This, coupled with the fact that many atypical forms exist even in normal tissues, complicates the matter considerably. Demonstration of the origin of plasma cells would help to clarify the question, but there is no general agreement on this matter with respect to either the typical or atypical forms.

Diagnosis. The diagnosis of multiple myeloma is at times very difficult. The manifestations of the disease often focus attention away from rather than toward the underlying cause. In a given case the true diagnosis may remain in doubt for some period of time, often to be decided only at necropsy. Geschickter and Copeland⁵ originally gave six cardinal diagnostic clinical signs of multiple myeloma, two or more of which they thought were usually present. These were "1, multiple involvement of the skeletal trunk in an adult; 2, pathologic fracture of a rib; 3, the excretion of Bence-Jones bodies; 4, characteristic backache with signs of early paraplegia; 5, an otherwise inexplicable anemia, and, 6, chronic nephritis with nitrogen retention, low blood pressure and high serum proteins." Since then, however, cases have been reported in which none of these features was present and several other characteristics have been described frequently enough to be important. These important features are: 1, hyperproteinemia with reversal of the albumin-globulin ratio;¹⁰ 2, hypercalcemia with normal or high serum phosphorus;^{6 12 15} 3, evidence of autohemagglutination in the counting chamber, on blood smears, or detected by the cayenne pepper appearance of blood in the small vessels of the fundus when viewed through the ophthalmoscope while pressure is being placed on the eyeball;⁴ and 4, the occurrence of an anticomplementary reaction when a complement-fixation test is carried out.⁷ That none of these signs is pathognomonic is obvious.

Early correct recognition of this disease is important since the predominance of certain of these features may lead to a mistaken diagnosis with an incorrect prognosis and at times futile diagnostic procedures or even fruitless surgical exploration, for example, search for parathyroid adenoma.^{2,12} The conditions with which confusion is commonest are metastatic skeletal lesions, hyperparathyroidism, spondylitis, nephritis and leukopenic leukemia. When localized rarefaction of bones has been found roentgenographically in available sites, direct biopsy of the lesion has been done. This is not always possible and even when possible the surgical procedure involved is often undesirable. More widely applicable is the method

of sternal aspiration. Because of its simplicity it is rarely, if ever, contraindicated.

The results of sternal aspiration which has been resorted to with increased frequency to assist in hematologic diagnosis within the past decade have been so satisfactory in cases of suspected multiple myeloma that Rosenthal and Vogel¹¹ stated: "A definite diagnosis is possible during life only when made by means of sternal biopsy or the more simple aspiration method of Arinkin." Scott¹⁴ reviewed reports in which sternal puncture showed a high proportion of myeloma cells and added 2 cases of his own. He concluded: "Sternal puncture thus affords a rapid and certain means of diagnosing myelomatosis, and many cases have been recorded where diagnosis would have been impossible without examination of the bone marrow."

Data on Cases Studied. In the past 2 years we have had an opportunity to study the 10 cases of multiple myeloma listed in Table 1. In each the condition was atypical in some way so that examination of the sternal marrow was desirable. In 4 cases, backache was the principal symptom; in one, cervical pain, and in one, arthralgia. Three of the patients sought medical attention because of symptoms associated with anemia. One of these also had fever and chills and one epistaxis and bleeding gums.

Only one patient (Case 8) did not have anemia. In the other cases the hemoglobin ranged from 5.5 to 11.2 gm. per 100 cc. and the erythrocyte count from 1,910,000 to 3,210,000 cells per c.mm. Examination of blood smears disclosed autohemagglutination in 7 cases. A leukemoid reaction was found in 4 of the cases and in 2 myeloma cells were seen in the peripheral blood.

In 7 cases the total serum protein was determined; in only one of these was it within the normal range of 6 to 8 gm. per 100 cc. of serum; in 6 the range was from 9.5 to 11.3 gm. per 100 cc. (Table 1). In the one case in which the serum protein was not elevated the albumin-globulin ratio was not reversed, while in the other 6 it was reversed. Bence-Jones protein was found in the urine in 6 cases. In one of these and in 2 cases in which Bence-Jones protein was not found it was sought for in the blood with negative results. The sedimentation rate was estimated in 6 cases (Table 1). In all of them it was elevated and in 5 of the 6 it was more than 125 mm. per hour (Westgren method). The increase in the serum protein and the increase in sedimentation rate were parallel.

In 7 of the 10 cases roentgenologic changes were recognized but in only 2 were they regarded as typical (Table 2). In one case generalized osteoporosis and pathologic fracture of one vertebra were found. In 4 it was impossible for the roentgenologist to express a definite opinion as to whether the changes were due to malignant metastasis or myeloma; in this group sternal aspiration was most valuable.

Results of Sternal Aspiration. A modification of Arinkin's method was used in performing the sternal aspiration.¹³ From 1 to 1.5 cc. of material was aspirated from the marrow cavity of the sternum and placed in a paraffin-lined test tube containing a small amount of heparin. Smears were made and stained with Wright's stain followed by Giemsa's stain. In those cases in which the nucleated cells were not abundant enough for convenient study, the material was concentrated by centrifugation in a Wintrobe tube and the "buffy" layer was used to make the smears.

TABLE 1.—FINDINGS IN PERIPHERAL BLOOD IN 10 CASES OF MULTIPLE MYELOMA.

Case.	Age (yrs.) and sex.	Auto- hemagglu- tination.	Total serum protein, mg. per 100 cc.	Albumin- globulin ratio.	Sedimen- tation rate, mm. in 1 hr.
1 . . .	51 M	+	11.2	1:2.8	140
2 . . .	61 M	+	11.3	..	158
3 . . .	62 M	+			
4 . . .	63 F	+	11.2	1:3.6	142
5 . . .	50 M	+	10.2	1:3.9	139
6 . . .	43 F	0	9.5	1:1.24	128
7 . . .	60 M	0	39
8 . . .	53 M	+			
9 . . .	60 F	0	6.3	2.39:1	
10 . . .	42 M	+	9.7	1:1.4	

Plasma cells make up less than 1% of the leukocytes in the material obtained from normal persons by sternal aspiration. These cells are morphologically identical with those seen in the peripheral blood. In 8 of our cases the aspirated marrow contained cells which resembled plasma cells in that the cytoplasm was deeply basophilic and the nuclei eccentric, but which differed from them in various ways. The size of these cells varied from that of a lymphocyte to cells having a diameter of 25 microns. In these cases the cells could be arranged in a series in which the differences between the cells from succeeding cases were slight, although the differences between the cells at the extremes of the series of all the cases were fairly great. A similar situation was found by Christian when he studied the cells in histologic sections. For the most part the cells in a given case were uniform in appearance, although in several of the cases they varied considerably.

TABLE 2.—STERNAL ASPIRATION AND ROENTGENOGRAPHIC OBSERVATIONS IN 10 CASES OF MULTIPLE MYELOMA.

Case.	Myeloma cells in marrow, %.	Roentgenologic findings.
1	7.3	Generalized osteoporosis and compression fracture of 1 vertebra
2	0.0	Absent
3	72.0	Absent
4	23.5	Question of myeloma or metastasis
5	2.0	Question of myeloma or metastasis
6	39.5	Probably metastatic
7	96.0	Metastasis
8	27.5*	Typical of multiple myeloma
9	11.5	Typical of multiple myeloma
10	51.0	Absent, but only ribs examined

* Typical plasma cells.

The most characteristic and readily recognizable of the cells encountered were those with an abundant, definitely outlined, deeply basophilic cytoplasm, a moderate-sized round, eccentrically placed nucleus having a fairly coarse chromatin which was sharply demarcated from the parachromatin, and a very large nucleolus. Some of these were present in all of the 8 cases and were designated myeloma cells (Fig. 1*a* and *b*).

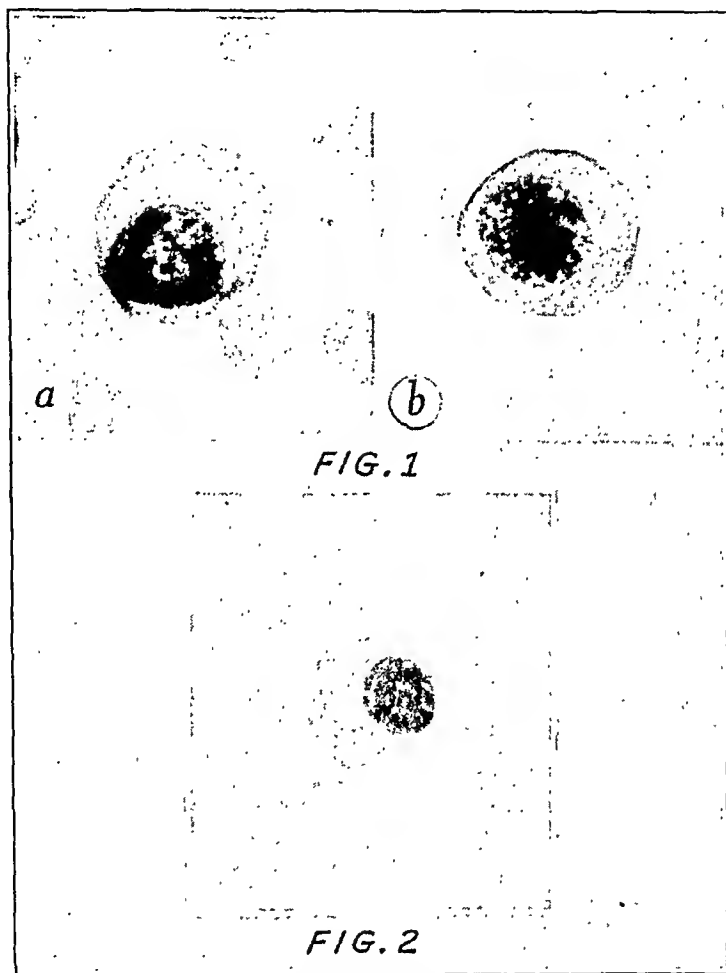


FIG. 1.—Myeloma cell. *a* (Case 3), apparently derived from stem cell (Wright-Giemsa stain, $\times 950$); *b* (Case 9), apparently derived from reticulo-endothelial cell (same stain and magnification).

FIG. 2.—Typical plasma cell from Case 8 (Wright-Giemsa stain, $\times 950$).

Minor variations from this description concerned all parts of the cell. The amount of cytoplasm varied from a narrow rim about the nucleus in some instances to a large quantity in others. Usually deeply basophilic it was at times somewhat lighter in color. Occasionally multiple small vacuoles were present, although characteristically the cytoplasm was clear or homogeneously granular. A perinuclear zone was not common. In most instances the cell membrane

was distinct and the outline round or oval, but an irregular shape did occur. The nucleus was always round and usually larger than that seen in typical plasma cells. The nuclear membrane was always distinct. The chromatin varied in its coarseness and pattern, but in no instances was it blocklike. In some of the cells it seemed to approach that seen in the stem cell (Figs. 1*a* and 3) while in 2 cases the nuclear pattern seemed more closely related to that of the reticulo-endothelial cell (Figs. 1*b* and 4). Though characteristically the cells contained a single large nucleolus, in some there were none and, in some, more than one. The size of a small number of the cells was huge with respect to both the cytoplasm and nucleus. Multiple nuclei occurred; instances of two, three and four nuclei of the type described were seen. Mitosis was encountered occasionally but was relatively rare.

The aspirated marrow in Case 8 contained an abnormally high percentage (27.5%) of plasma cells (Fig. 2). They had an abundant deeply basophilic cytoplasm with an eccentrically placed small nucleus containing coarse clumps of chromatin; a few cells with somewhat larger nuclei, but not nucleoli, were seen.

Cells resembling the ones described were not encountered in the sternal marrow in Case 2, and the plasma cells were not increased in number. This is not an inconsistent finding, and indicated that the sternal marrow was not yet involved.

Thus in our cases the cells which resembled plasma cells ranged in appearance from those identical with the plasma cell seen in the peripheral blood and normal bone marrow to the characteristic myeloma cell. We have found identical cells in imprint preparations and dry smears of tissue obtained from direct biopsy of a lesion or from necropsy in other cases in which the lesions were typical examples of multiple myeloma histologically. One reason for designating the cell with a large nucleolus a myeloma cell is the fact that we have not found it to be present in bone marrow from any of the other conditions which we have studied in the course of diagnostic examinations of sternal marrow in 160 instances.

Summary and Conclusions. Myeloma has been suspected and sternal aspiration has been valuable in cases in which one of the following features was encountered: unexplained anemia with malnutrition; unexplained pain in the bones with absence of any abnormality in the roentgenograms; roentgenographic findings indicating the possibility of metastasis to bone without obvious primary malignancy; evidence of nephritis with hyperproteinemia; hyperproteinemia without nephritis; questionable hyperparathyroidism, and evidence of autohemagglutination in the blood smears or in the circulation of the eyegrounds.

Sternal aspirations were carried out in 10 cases in which the diagnosis of multiple myeloma was strongly suspected. In 8 cases myeloma cells were found. In one an increased proportion of the

marrow cells were plasma cells. In one case the material obtained was not abnormal. The following conclusions seem warranted:

1. The presence of myeloma cells in bone marrow obtained by sternal aspiration is pathognomonic of multiple myeloma.

FIG. 3



FIG. 4

FIG. 3.—Representative field from Case 3. Origin from stem cell is suggested. Autohemagglutination is evident (Wright-Giemsa stain, $\times 950$).

FIG. 4.—Representative field from Case 7. Note eccentrically placed nuclei and large nucleoli with fairly abundant cytoplasm. The character of the chromatin suggests origin from the reticulo-endothelial cell (Wright-Giemsa stain, $\times 950$).

2. An increase in the proportion of typical and atypical plasma cells found is suggestive of multiple myeloma.

3. The absence of abnormal findings in the sternal marrow does not rule out the diagnosis.

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THE ACTION OF THE ANTIPERNICIOUS ANEMIA PRINCIPLE ON THE BLOOD PICTURE OF OPOSSUM POUCH-YOUNG AND RAT EMBRYOS.*

BY JULES H. LAST, PH.D.,

RESEARCH ASSISTANT IN DEPARTMENT OF PHARMACOLOGY,

AND

EDWIN E. HAYS, M.S.,

RESEARCH ASSISTANT IN DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CHICAGO, CHICAGO, ILLINOIS.

(From the Departments of Pharmacology and Biochemistry, University of Chicago.)

THE only method of measuring potency of liver preparations is the clinical assay on "suitable," uncomplicated pernicious anemia patients in a state of relapse. The disadvantages in having to depend on the fortuitous appearance of an ever-decreasing number of satisfactory pernicious anemia cases at certain hospitals and clinics for the quantitative assay of a drug are immediately apparent. The present U.S.P. unit of potency for liver preparations is defined on the basis of the remission of the blood picture in "suitable" patients. The unit is vague and unsatisfactory.

Space does not permit a critical discussion of the numerous, biologic tests proposed, but with few unconfirmed exceptions^{4,5,9} none would serve as a valid indicator for the potency of liver preparations. Of special interest have been the reports that antipernicious anemia (A-P-A) principle accelerates the maturation of embryonic blood elements. In 1880, Ehrlich pointed out that the morphologic identity of the erythroid cells of the primitive, prehepatic generation of red cells in the embryo and the megaloblastic generation of red cells characteristic of untreated pernicious anemia. He postulated erythropoiesis in pernicious anemia to be an embryonal reversion. At present it is believed that the red cells of the primitive generation in the embryo though morphologically similar are not identical with the megaloblastic generation of pernicious anemia.^{6a}

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The possibility that embryonic and megaloblastic erythropoiesis might respond in a similar manner to liver therapy has stimulated interest in the fetal approach to the bio-assay problem.¹⁵

In 1928, it was reported that blood island maturation in early chick blastoderms was accelerated by the addition *in vitro* of liver preparations.³ This work could not be confirmed.⁷ The injection of liver extracts into the unincubated egg does not change the blood picture of the developing chick embryo before and during the anlage of the bone marrow.¹⁰ The blood picture in the rabbit fetus has been reported unaffected by the A-P-A principle.¹⁶ It has recently been reported that the injection of anti-anemia principles does alter the blood picture of opossum pouch-young.^{12a,b} Extensive studies have been reported on the response of the new-born rat whose mother was treated with anti-anemia substances. Accelerated maturation has been observed^{1,11,13} but has not been confirmed.^{2,8,14} Recent observations of accelerated maturation of primitive erythropoiesis in the yolk sac of the 11-day rat fetus subsequent to liver and ventriculin therapy in the pregnant rat emphasize the necessity of studying the prehepatic, "megaloblastic" generation of cells.^{6b,c}

The positive findings in the opossum pouch-young and 11-day rat has prompted further study of the embryo with the view of developing a method of bio-assay for the antipernicious anemia principle.

Methods. United States Bureau of Standards hemocytometers and Trenner automatic red cell pipettes were used for red blood cell counts. Hayem's solution was the standard diluent. Three-tenths per cent brilliant cresyl blue in isotonic salt solution was used as the diluent and stain for reticulocyte counts. The Newcomer method was used for hemoglobin determinations. Van Allen tubes were used for hematocrit determinations with heparin as the anticoagulant. All dry blood smears were stained with May-Grünwald-Giemsa stain.

In the opossum work, 45-day-old pouch-young, about 65 mm. long (snout-rump length), were injected subcutaneously with daily doses of 3 units of a potent liver preparation, for 7 to 9 days.* The young remained attached to the maternal nipple throughout the injection period. Controls consisted of litter mates either uninjected or receiving an inactive liver preparation (70% alcohol insoluble fraction).† Due to the size of the animals it was necessary to decapitate the young to obtain blood samples for red cell counts and hematocrit determinations. The mother opossums were maintained on a diet of raw meat, fox chow pellets, and water.

In the rat work, young adult female rats from our stock colony (mixed strain) were mated and on the twentieth, fifteenth and eleventh day of pregnancy the fetuses were removed under ether anesthesia with the amnion, yolk sac, and placental button intact. Decapitation of 20-day fetuses was employed to obtain blood samples. Mean corpuscular volumes of the red cells were calculated from red cell counts and hematocrit readings. Blood from the 15-day fetuses was obtained by puncturing the vitelline vessels lying on the yolk sac. The circulating blood of the 15-day fetus is comprised predominantly of erythroblasts, normoblasts, non-nucleated reticulocytes and erythrocytes of the prehepatic generation. Therefore,

* Generously contributed by Dr. Guy Clark of Lederle Laboratories.

† Obtained through the kindness of Armour Laboratories.

accelerated maturation of primitive erythropoiesis reported in the 11-day fetus should appear in a study of the blood of the 15-day fetus. Since the percentage of non-nucleated cells rises rapidly between the fourteenth and eighteenth days of fetal life, a significant increase above the control percentage value at 15 days represents accelerated maturation of primitive erythropoiesis. One sample of blood was smeared, dried, and stained as described above. Supravitaly stained wet preparations were also made by mixing another drop of blood with 0.18% brilliant cresyl blue in isotonic salt solution. One thousand cells per fetus were counted, 500 on a wet preparation and 500 on a dry smear. The choice of 4 fetuses yielded a representative sample of a litter. The weight of each fetus was recorded, since the body weight was considered the most accurate gross measure of fetal development in the rat.

The small size of the 11-day embryos required the use of a binocular dissecting microscope to free them from their membranous investments. Blood smears were made from heart blood and stained in the usual manner. The circulating red blood cells of the 11-day rat fetus are, for the most part, immature basophilic cells of the primitive generation. As maturation and mitosis occur intravascularly, the cytoplasm becomes polychromatophilic and hemoglobiniferous. Concurrently there is a marked decrease in nuclear size with condensation of nuclear chromatin. A significant decrease in nuclear diameter would be indicative of accelerated maturation of primitive erythropoiesis. Nuclear diameters were measured by means of a camera lucida. Again, 4 embryos per litter were used and 50 cells per embryo were measured.

In the 20-day embryo group, the liver-treated animals received 7.5 u. on the first day of pregnancy, 7.5 to 15 u. on the ninth, tenth or fourteenth day, and a 1.5-u. daily maintenance dose. The rats received a total of 41.5 to 49 U.S.P. units during the 20-day period of pregnancy. The mother rats in the 15-day group were usually given 3.5 to 7.5 u. on the sixth day of pregnancy and maintained on 1.5 u. daily through the fourteenth day. Rats on a 31-u. level received 7.5 u. on Days 6, 7, and 8, with subsequent 1.5-u. maintenance dose daily. Total doses varied from 9 to 31 U.S.P. units per rat. In the 11-day group, the rats received 12 to 75 u. during the eighth, ninth, and tenth days of pregnancy. In this group pregnant rats were also fed fox chow checker diets containing 2.5% Ventriculin by weight. This dosage has been reported as optimal for accelerating maturation of the primitive generation in the 11-day embryo. All pregnant rats were treated with potent anti-anemia preparations before, during, and after the anlage of the mesoderm which gives rise to the blood-forming tissues in the embryo. With the exception of the 11-day group which was fed a fox chow checker diet, the 20- and 15-day groups were fed a stock ration of corn meal, powdered milk, raw meat, bone meal and fresh water.

Results. The blood values of 27 opossum pouch-young are listed in Table 1. The mean corpuscular volumes of the red cells compare favorably in the animals receiving potent liver therapy, inactive liver preparations, and no injections. There is also no appreciable change in the red cell count. The series of animals is of necessity small, due to the difficulties in obtaining opossums from the South and to the fact that the animals breed only in the spring of the year. Contrary to positive reports, no accelerated maturation of the blood picture as reflected by a significant decrease of the mean corpuscular volume of the erythrocytes was observed in the pouch-young receiving liver therapy.

TABLE 1.—THE RESPONSE OF OPOSSUM EMBRYOS TO LIVER THERAPY.

Therapy.	No. of embryos.	Length* (mm.).	Weight (gm.).	R.B.C.†	Hemato-crit.‡	M.C.V.§
Controls (initially removed)	6	64	8.2	2.55	30.1	118.7
Controls (uninjected)	2	73	...	3.25	35.2	109.2
Liver extract (inactive)¶	6	75	12.1	2.49	31.5	126.4
Liver extract (Lederle)	13	76	12.4	2.70	30.8	112.3

* Snout-rump length (mean).

† Erythrocytes in millions per mm.³ (mean).

‡ Per cent packed erythrocytes (mean).

§ Mean corpuscular volume in cubic micra (mean).

¶ 70% alcohol insoluble fraction.

The lack of a response to the A-P-A factor in the normal 20-day rat fetus is illustrated in the summary of 46 fetuses in Table 2. The red cell counts and mean corpuscular volumes of the treated animals compare favorably with the uninjected controls.

TABLE 2.—EFFECT OF LIVER EXTRACT ON THE BLOOD PICTURE OF 20-DAY RAT EMBRYOS.

Therapy.	Litters.	Fetuses.	R.B.C.		Hematocrit.		M.C.V.	
			Mill.*	σ.	%†	σ.	μ ³ ‡	σ.
Controls (uninjected)	4	22	1.95	0.73	36.9	4.9	189.0	18.4
Lederle liver extract, 41.5-49 U.S.P. units	5	23	2.12	0.25	38.5	3.1	185.0	11.5

* Erythrocytes in millions per mm.³ (mean).

† Per cent packed erythrocytes (mean).

‡ Mean corpuscular volume in cubic micra.

In the large series of 15-day rat embryos studied, considerable variation in the development of embryos was observed. Figure 1 illustrates the per cent non-nucleated cell values as plotted against fetal weight.

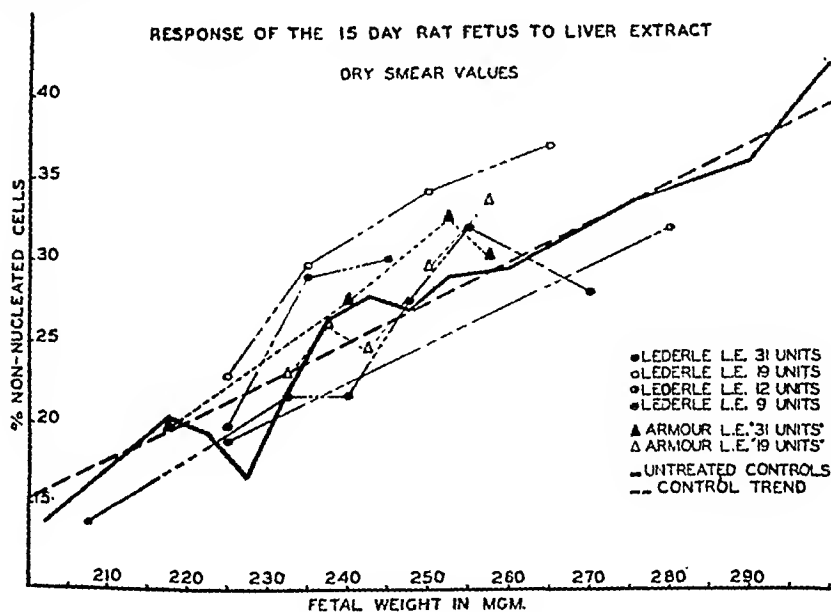


FIG. 1.

Is the response of the animals receiving liver therapy biologically significant? The distribution of variation of the control animals contains two components, *i. e.*, the variation at any given fetal weight and the upward trend. Since the trend factor is fortuitous

and unnecessary for comparison of a treated and untreated animal at any given fetal weight, it can be eliminated. By fitting a straight line to the control curve by the least squares method and by calculating the distribution of variation of control values from the straight line, the standard deviation can be determined independently of the trend. The means of per cent counts on treated and untreated animals as compared with the means of the calculated normal response determined from the straight line equation are listed in Table 3. In no instance does a mean of a treated group of rats exceed the calculated control value by the conventional two sigma.

TABLE 3.—COMPARISON OF DIFFERENTIAL COUNTS ON TREATED AND CONTROL 15-DAY RAT EMBRYOS.

Therapy.	Litters.	Fetuses.	Mean fetal weight (mg.).	Per cent non-nucleated cells (mean values).			
				Wet smears.		Dry smears.	
				Expt.	Calc.†	Expt.	Calc.†
Controls (untreated)	30	120	240	22.4	22.4	26.2	26.3
				$\sigma = 3.3$		$\sigma = 4.4$	
Lederle liver extract:							
A. 9 units	3	12	240	19.6	22.2	18.7	25.8
B. 12 units	3	12	240	20.1	20.7	26.4	23.8
C. 19 units	6	24	240	25.9	22.1	30.0	25.4
D. 31 units	9	36	240	21.8	22.6	25.3	26.5
Armour liver extract:							
A. "19 units"*	8	32	240	26.4	22.6	26.5	25.4
B. "31 units"*	7	28	250	29.9	24.6	32.0	28.6

* A unit equivalent to 15 gm. of fresh beef liver.

† Means of values calculated from straight line equation fitted to control data by the least squares method where x = fetal weight and y = per cent non-nucleated cells.

To obviate the criticism that in a study of the 15-day embryo one would not observe the effects of the A-P-A principle on the primitive generation, it was necessary to investigate the effect of liver and Ventriculin on the immature primitive cells in the 11-day rat embryo. Table 4 summarizes the response of the 11-day embryo to anti-anemic therapy.

TABLE 4.—NUCLEAR DIAMETERS OF TREATED AND CONTROL 11-DAY RAT EMBRYOS

Therapy.	Litters.	Embryos.	Nuclear diameters (μ -average).
Controls (untreated)	12	50	8.5
Ventriculin*	7	28	8.4
Lederle liver extract:			
A. 12 units	4	19	8.6
B. 37 units	1	4	8.5
C. 45 units	1	4	8.5
D. 52 units	1	4	8.2
E. 60 units	4	16	8.3
F. 75 units	1	4	8.5

* Added as 2.5% of fox chow chequer diet.

In no cases is there a significant decrease in the nuclear diameters of a treated group of embryos over controls.

Discussion. The lack of a response of the opossum pouch-young and the rat embryo to the A-P-A principle necessitates a more critical evaluation of the fetal approach to the bio-assay problem. Since A-P-A factor is ineffective in altering the embryonic blood picture, either the embryo does not require the A-P-A principle, or

it receives a sufficient supply from maternal stores, or it manufactures its own supply *de novo*. The assumption of placental transfer of the A-P-A factor though probable from indirect evidence is still open to question.

The fallacy in the rationale of the fetal approach is to disregard the past history of the erythrocytes in comparing the blood picture of the embryo with that of a pernicious anemia patient receiving liver therapy. The macrocytes in the blood of pernicious anemia reflect a megaloblastic erythropoiesis which is an abnormal process. The large primitive erythrocytes in embryonic blood are the mature elements of primitive erythropoiesis which is a normal physiologic process. Furthermore, the immature cells of the primitive embryonic and megaloblastic generations are not cytologically identical.

It is difficult to reconcile the positive findings in the opossum pouch-young with those of the 11-day rat embryo. In the 11-day rat embryo, A-P-A factor might conceivably accelerate the intravascular maturation, of the immature primitive erythroblasts. In the 45-day opossum, the primitive generation has matured to the erythrocyte stage and is rapidly being replaced by small definitive red blood cells. Thus, any changes appearing in the peripheral blood must be due to the action of the A-P-A factor on the bone marrow or liver. No histologic evidence has been presented to indicate any stimulation of definitive erythropoiesis in opossum pouch-young or new-born rats. It has been conclusively demonstrated that the A-P-A factor does not affect definitive erythropoiesis in the normal animal. Furthermore, the response reported in opossum young is non-specific, in that gastric juice which is ineffective in the treatment of pernicious anemia also elicits a response in the opossum.

No explanation can be offered for the discrepancy between our findings and those in the literature on the opossum pouch-young and the 11-day rat embryo. The results of our experiments on the 20-, 15- and 11-day rat embryo and opossum pouch-young are in agreement with the findings of other workers who failed to detect any response of the normal mammalian embryo to anti-anemia therapy.

Summary. 1. Potent, standardized anti-anemia preparations were injected into or fed to pregnant rats and 45-day opossum pouch-young. Rats received therapy before, during, and after formation of the anlage of the mesoderm in the developing embryo.

2. No evidence of accelerated maturation as reflected by changes in the red cell count or mean corpuscular volume following liver therapy was observed in a study of 27 opossum pouch-young and 46 20-day rat embryos.

3. In a series of 264 treated and untreated 15-day fetuses from 66 litters of normal rats, statistical analysis of the data indicates the response in liver-treated animals to be within the range of biologic variation.

4. Liver and Ventriculin therapy did not alter the maturation rate of the primitive generation of red cells in 132 11-day rat embryos studied.

5. Embryogenesis of blood in the opossum and rat is unaffected by the antipernicious anemia principle and therefore neither opossum pouch-young nor rat embryos should be used to bio-assay anti-anemia preparations.

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ADDENDUM: After this manuscript was submitted for publication, a paper by O. P. Jones appeared (Arch. Int. Med., 68, 476, 1941) questioning the lack of response of the 15- and 11-day embryos to anti-anemic therapy in the pregnant rat. The study of the 15-day rat embryo was criticized because "changes in the cells of the prehepatic generation are apt to be attenuated or completely masked by the rapidly growing normoblastic generation." This criticism, however, is apparently unsubstantiated by experimental facts. The circulating blood cells of the 15-day embryo are predominantly primitives of the prehepatic generation with relatively few definitives of the normoblastic generation. Since the maturation rate of both generations of embryonic red cells in the rat has been reported to be accelerated by anti-anemic therapy, the 15-day embryo should reflect changes in either or both generations of cells. Furthermore, hematopoietic responses in the 15-day embryo can be more easily and accurately determined in contrast with the tedious, impractical method of measuring the diameters of hundreds of cells in the 11-day embryo. However, no marked changes were observed in the blood pictures of either 15- or 11-day rat embryos after injection of potent anti-anemic preparations or the feeding of Ventriculin to pregnant rats.

As additional evidence that primitive prehepatic erythropoiesis can be altered by the anti-anemic principle, Jones quotes extensively the work of Sabin wherein the addition of liver extracts to chick blastoderms *in vitro* appeared to accelerate the maturation of the prehepatic embryonic red cells. Reference to the later work of Muller was omitted. Muller, with Sabin's assistance, failed to confirm Sabin's preliminary work on chick blastoderms.

The entire magnitude of the response to Ventriculin therapy in treated animals as reported by Jones was 5% or less. With a response of 1% to 5% it is necessary to evaluate critically the control line above which the response occurred. Jones' data are conspicuously lacking in adequate controls. In fact, it is difficult to ascertain what or where the controls are. No information as to the number of control animals is given. A textual reference to 5 rats is made with the statement, "This series could not be used in the present quantitative study because there were differences in time of mating the rats, their diets, and the method of sampling blood from the embryos." With no adequate control data the validity of 2% or 5% response based on data from 2 to 3 rats per dosage level is open to serious question. The value of such a response as a quantitative measure of the potency of anti-anemic preparations is questionable, especially when one considers that biologic variation in a large series of animals is conservatively estimated at 10% and that in most U.S.P. bio-assay methods a variation of $\pm 20\%$ of the standard is permissible.

Assuming that the "response" does occur, it cannot be concluded that the slight changes noted were due to the antipernicious anemia principle. The lack of adequate control experiments wherein other tissue extracts, prepared in a manner similar to Ventriculin concentrate, would be both injected and fed to pregnant rats makes it difficult to draw valid conclusions concerning specificity of Jones' observations.

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THE EFFECT OF LIVER EXTRACTS UPON ERYTHROPOIESIS IN THE CHICK EMBRYO.*

BY EDWIN E. HAYS,

RESEARCH ASSISTANT IN BIOCHEMISTRY,

JULES H. LAST,

RESEARCH ASSISTANT IN PHARMACOLOGY,

AND

F. C. KOCH,

FRANK P. HIXON DISTINGUISHED SERVICE PROFESSOR EMERITUS OF BIOCHEMISTRY,
DEPARTMENTS OF BIOCHEMISTRY AND PHARMACOLOGY, UNIVERSITY OF CHICAGO,
CHICAGO, ILL.

THE concept that the red cells in pernicious anemia are morphologically similar to those found in the embryo has been the basis of several attempts to^{4,6,12} devise an assay method for the antipernicious anemia factor.

The embryonic chick has the advantage that it is possible to direct the active liver fraction to the embryo itself without depending upon placental transfer, and the uncertainty of absolute age of the embryo, as is the case in mammalian studies, is practically eliminated. The erythropoietic organ, the yolk sac, is also readily available for study in contrast to that in mammals. The availability of the experimental animal cannot be overlooked.

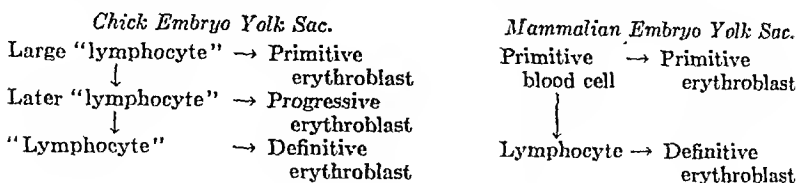
Reimer⁹ studied the 9- to 15-day embryo. In his hands small doses had no effect upon the formation of erythroid elements in the bone marrow. Sabin,^{10a} using *in vivo* mounts of 3-day chick embryos, reported that active material prepared by Cohn caused a second division of primitive megaloblasts in the blood islands. Muller⁸ failed to confirm this finding.

These considerations led us to undertake the study of various potent liver fractions upon the chick embryo during the formation

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of the definitive, or mature, generation of red blood cells and their replacement of the primitive generation in the circulating blood and/or effect upon the blood at the site of its formation in the blood islands of the yolk sac.

According to Dantschakoff¹ the comparison between chick and mammalian erythropoiesis is indicated by this diagram:



The early forms of the primitive erythroblast are the cells regarded as morphologically similar to the megaloblast found in human pernicious anemia. Clear-cut differentiation of primitive erythroid types in the yolk sac is admittedly difficult and hence the possibility of changes in the yolk sac being reflected in the circulating blood was examined first.

From Sabin's¹⁰⁶ studies on *in vivo* mounts, it is known that granulocytes begin to wander into the circulating blood after the third day of incubation, the circulating lymphocytes (mature lymphocytic elements as contrasted with the erythroid elements of Dantschakoff) appear during the fourth day. These cells occur in small clumps in whole blood smears and should be readily distinguished from immature red cell forms.

If an acceleration in the rate of maturation or production of the definitive generation could be produced as a specific result of the injection of anti-anemia preparations, this change might be observed in the circulating blood at the proper transitional stage as well as in the yolk sac itself. This type of transformation is considered by some to be the mechanism involved in the response by anemia patients to liver extract.

If the circulating blood does not show any change, then the cytologic structure of the cells in the yolk sac might indicate whether there has been a stimulation in the production of the more mature cells without their release into the blood stream.

Methods. Injection. All injections were made under sterile conditions in a tissue-culture transfer chamber. The egg was placed with its pointed end upwards and after carefully wiping with 70% alcohol was pierced with a sterile lancet. The liver extract was injected directly into the egg white by means of a syringe through a short needle. After injection, the hole was sealed with boiled paraffin having a melting point between 50° and 55° C. The volume injected varied from 0.05 to 0.5 cc., however the majority of injections were 0.2 cc. All samples were rendered phenol-free by repeated vacuum concentration and dilution with water and were sterilized by means of a pressure Seitz filter.³ Fertile Redrock eggs were used and were incubated at 102° F. in a constant temperature incubator.

Preparation of Smears and Yolk Sacs. The eggs were candled and set so that the embryo floated on top and the shell carefully chipped away in

order to expose the *area vasculosa* without breaking the yolk sac. A large vessel, preferably an artery, was carefully pricked with a fine needle and the blood drawn into a capillary pipette. Smears were made in triplicate using the slide and coverslip method and were stained with May-Grünwald-Giemsa stain. Five hundred consecutive cells were counted on each slide.

In later studies, after obtaining the blood sample, portions of the yolk sac were excised, spread on a small watch-glass, and immediately fixed with Zenker-formalin for 20 minutes. These were stained with hematoxylin-eosin-azure II according to the technique of Maximow, as described by Loosli.⁷ They were mounted in balsam.

Means of Evaluation. The possibilities for an evaluation of the preparations were: 1, the determination of the rate of maturation of the red cells of the different generations; and 2, the histologic differentiation of the cells in the blood-forming organs.

The method most practical for determining an increased maturation of red cell types in the circulating blood was that of differential cell counts upon smears. Since the definitives are easily distinguished from the primitives in such smears, an increase in their concentration at a given stage should indicate an increased formation with a corresponding increased maturation of the primitives which they replace. The source and cause of the difference could be determined in the yolk sac preparations.

In all cases the embryos were weighed in order to determine age.

Experimental. Preliminary studies showed that the definitives occur only occasionally in the circulating blood before 4½ days of incubation and that their replacement of the primitives may be indicated by the percentage of definitives in the total number of cells. Hence, the 5 days' incubation was chosen as best suited for our study.

Doses of 7 human units injected before incubation produced a pronounced increase in definitives over the untreated controls. Different commercial liver preparations of known therapeutic activity were injected at different levels. Extracts prepared from heart muscle and yeast were also used. Table 1 summarizes the results.

TABLE 1.—ERYTHROPOIESIS IN CHICK EMBRYOS INJECTED BEFORE INCUBATION.

Extract.	No. of units.	Total solids (mg.).	No. of embryos.	Average weight (mg.).	% embryos with over 50 definitives per 1000 cells.	% "response."*
None (controls)	160	182	11	
Saline	13	186	8	
Bacto-peptone	145.0	13	188	39	255
Difco Beef Extract	112.0	5	181	20	8
		66.2	6	184	0	
Yeast	118.0	5	190	0	
Whole stomach	63.0	15	176	36	227
Heart	64.5	8	183	12	
Lederle Liver Extract	2.0	15.9	20	194	10	
Lot No. 381H243S	3.0	26.0	7	178	35	218
	5.3	47.1	26	180	45	309
	7.1	58.0	57	177	51	364
	11.3	96.2	4	178	50	355
	13.5	113.0	12	175	50	355
	15.0	130.2	7	176	84	684
	18.0	181.5†				
Abbott	7.5	78.0	11	176	55	400

* Percentage over controls obtained by subtracting 11 from the value and dividing by 11.

† All died.

In an attempt to decrease the dosage required per chick embryo, injections were made directly on top of the area vasculosa at various stages of incubation. Injection at the third day of incubation appeared to give the best response. Table 2 summarizes the results.

TABLE 2.—ERYTHROPOIESIS IN CHICK EMBRYOS INJECTED ON THIRD DAY OF INCUBATION ON AREA VASCULOSA.

Extract.	Total solids (mg.).	No. of embryos.	Average weight (mg.).	% over 50 definitives per 1000 cells.	% "response."
None (controls)	158	179	14	
Saline	22	164	21	50
Yeast	2.2	5	178	60	328
	6.0	6	185	50	257
Heart muscle	1.1	7	190	70	400
Lederle Liver Extract, Lot No. 381H335B	1.0	4	172	100	614
	2.4	7	160	42	200
	3.7	6	170	66	371
	5.0	6	184	0	
	9.5	19	177	75	435
Same in saline	0.1	10	182	20	43
	1.0	3	190	66	371

It is apparent from Tables 1 and 2 that the response is non-specific and erratic. The question arises as to the significance of the values noted in Table 1. If the frequency of distribution is plotted for all 551 control smears, Table 3 results. According to

TABLE 3.—FREQUENCY OF DISTRIBUTION IN 551 CONTROL SMEARS.

No. of definitives per 1000 cells.	% of total number of cells.	No. of definitives per 1000 cells.	% of total number of cells.
0	5.7	41- 50	3.8
1-10	40.8	51- 60	3.4
11-20	19.3	61- 70	2.2
21-30	10.5	71-100	2.2
31-40	10.2	>100	2.1

Fisher² only experimental values which lie outside of the range which includes at least 90% of all the control values are statistically significant. Applying this criterion to the above series of controls only smears having counts greater than 50 definitive generation cells per 1000 might be significant. This criterion eliminates most of the values listed in Tables 1 and 2. It is also obvious that the response is non-specific and not of quantitative value.

However, to strengthen the evidence that the above responses were not due to the antipernicious anemia principle, more purified fractions were made from liver extracts of tested potency, following techniques of Laland and Klem⁵ and Sladek and Kyer.¹¹

These fractions, together with others recorded in Table 4, were injected before incubation. These negative results give additional evidence as to the non-specificity of the response observed.

TABLE 4.—EFFECT OF LIVER FRACTIONS ON ERYTHROPOIESIS IN CHICK EMBRYOS INJECTED BEFORE INCUBATION.

Extract.	No. of units.	Total solids (mg.).	No. of embryos.	Average weight (mg.).	% over 50 definitives per 1000 cells.	% "re-sponse."
None (controls)	235	176	14	
Armour Lot 17	2.0*	125.0	8	173	0	
Armour Lot 29	7.0	127.0	4	170	50	257
Fraction 5	9.7†	38.8	5	181	0	
Fraction 6	12.2†	73.4	15	178	18	3
Fraction 1A6	10.2†	102.0	16	174	40	186
Lederle Liver						
Lot 381H304A	10.3	67.0	6	171	16	1
Lot 381H335B	6.5	56.4	18	177	28	100
	11.0	93.0	12	184	16	1
	14.2	122.6	16	179	24	7
Lot 381H243S	7.2	58.6	15	175	62	343
Fraction 1L7	..	48.4	8	173	12	
Wilson	7.7	93.0	0†			
Lilly	8.4	112.6	2†			
Armour Lot 96	7.7	101.5	0†			

* Highest non-toxic dose.

† Calculated from clinical assay.

‡ Toxic.

Yolk Sac Studies. Yolk sac preparations also were made of from 3- to 5½-day embryos at 12-hour intervals of uninjected controls and eggs injected with 10 human units before incubation. There was no clear-cut difference between the injected and the control preparations although the cell counts upon the blood smears showed 80% to have over 50 definitives per 1000. There was no increase in the number of more mature cell types present nor an earlier appearance of definitive cells. In some preparations there appeared to be an increase in the percentage of the definitive types, but this finding was not consistent in other preparations and in those taken from embryos 12 hours later.

Camera lucida measurements of the mean nuclear diameter of the red cells in blood smears taken from these injected chick embryos showed no significant changes as compared with the controls.

It appears from these studies that the occurrence of the definitives in the circulating blood was largely a pouring-out effect and not a specific stimulation of red cell formation or maturation.

Summary. 1. Injection of eggs prior to incubation with liver extracts containing 7 or more human antipernicious anemia units produced an increase in the number of early adult cells in the circulating blood of the 5-day chick embryo.

2. Injection prior to incubation with saline and extracts prepared from heart muscle, yeast, whole stomach, and with commercial beef muscle and peptone preparations produced little or no increase in the number of these cells.

3. Injection at the third day of incubation with yeast and heart extracts, saline, as well as low doses of liver extracts, produced a non-specific and irregular increase in the number of these cells in the 5-day chick embryo.

4. Injection prior to incubation with more purified liver extracts

produced no increase in the number of these cells in the circulating blood of the 5-day embryo.

5. Injection prior to incubation with active liver extracts failed to produce a significant change in the mean nuclear diameter of the cells circulating in the blood of the 5-day chick embryo.

6. Study of the yolk sac preparations of these embryos showed no consistent change in the rate of maturation or formation during erythropoiesis in the yolk sac indicating that the response noted in the injected embryos was due to a pouring out of these immature forms.

7. Statistical analysis of the data showed that the response obtained was not significant.

Conclusion. Erythropoiesis in the 3- to 7-day-old chick embryo cannot be utilized as a specific means of assay for the antipernicious anemia potency in liver extracts.

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ACETYLPHENYLHYDRAZINE ANEMIA.

2. BILE PIGMENT ELIMINATION AND NEW HEMOGLOBIN RECONSTRUCTION IN THE BILE FISTULA DOG.*

By WALTER O. CRUZ, M.D.,†

VISITING FELLOW OF THE ROCKEFELLER FOUNDATION, SCHOOL OF MEDICINE AND DENTISTRY, PATHOLOGY DEPARTMENT,

WILLIAM B. HAWKINS, M.D.,

ASSOCIATE PROFESSOR OF PATHOLOGY,

AND

GEORGE H. WHIPPLE, M.D.,

PROFESSOR OF PATHOLOGY,

ROCHESTER, N. Y.

(From the Department of Pathology, The University of Rochester School of Medicine and Dentistry.)

DESTRUCTION of red blood cells in the circulation presents many fascinating problems for consideration. We know much about this reaction in animals and human beings. When red cells disintegrate

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† On Official Commission from the Instituto Oswaldo Cruz, Rio de Janeiro, Brazil.

we believe that *three important fractions* of hemoglobin are set free, perhaps largely through the activity of the reticulo-endothelial system. From hemoglobin are derived a pigment radicle (pyrrol aggregate), globin and iron. The *iron* is saved with meticulous care and only traces escape in the bile and urine.² The *globin* probably can be used in the production of new hemoglobin^{12b} and perhaps for other purposes related to protein metabolism in the body. The *pigment radicle* is discarded and appears almost quantitatively (80% to 100%) as bile pigment in the bile and urine.^{4,6,14} Some observers¹⁰ claim that the pigment radicle is re-utilized to form new hemoglobin and this seems a sensible response but the body of the dog at least does not choose this course. Therefore, we question the claims that the human patient can use bile pigment to aid in the production of new hemoglobin.

When acetylphenylhydrazine in the doses given is used to destroy red cells in the circulation, we note in Table 1 that the surplus bile pigment amounts on the average to 88% of all theoretical pigment from the calculated red cells—that is essentially a quantitative elimination of the pigment radicle of the destroyed hemoglobin. Within the body the recovered iron and probably some of the globin are used promptly to form new hemoglobin for new red cells which appear in great numbers. In fact, these bile fistula dogs regenerate close to the expected maximum of new red cell production. By means of standardized anemic dogs it has been shown in this laboratory^{12a} that a 10-kilo dog in health, with maximal anemia stimulus, given large doses of iron and favorable protein (liver) can produce 70 gm. of hemoglobin in new red cells per week. Dog 37-137 (Table 1), weight 10 kilos, produced about 120 gm. of hemoglobin in approximately 2 weeks (Table 2). Obviously, if the dog throws away the *pigment radicle* it can readily be produced to supply the demand for new hemoglobin. It has been suggested that the dog forms these pyrrol rings in considerable amounts (300 to 400 mg. daily) and must obtain them from protein stores or perhaps by closing a straight chain amino-acid (glutamic acid for example).

Recent observations¹ indicate that these doses of hydrazine in dogs will injure *all red cells* except the young reticulocytes and obviously these injured cells all disintegrate and free hemoglobin to contribute the recorded amounts of bile pigment. Injury of red cells is recognized by the presence of Heinz corpuscles within the red cell protoplasm.

Methods. All of the dogs studied had the *gall-bladder renal* type of fistula as devised by Kapsinow, Engle and Harvey.⁸ The dogs are kept in galvanized iron metabolism cages and the urine-bile mixture is collected over 24-hour periods. Chloroform (5 cc.) is put in the collection bottle as a preservative. The dogs are fed the *salmon bread diet* because its hemoglobin building properties have been thoroughly studied. Since it is a diet low in fat and rich in carbohydrate, it is well tolerated by these bile-deprived dogs. It is in itself a complete diet and its preparation has been previously described.¹⁷

In order to prevent the intoxication^{5,7} that results from complete bile deprivation, the dogs are given dog bile or ox bile (50 cc.) on the food daily.

The method⁹ for the determination of bile pigments in the urine has been described in detail in a previous publication. It has been customary to use the ratio 40 mg. of bilirubin = 1 gm. of destroyed hemoglobin since the pigment radicle comprises 4% of the hemoglobin molecule. However, the formula of bilirubin is now better established and it is considered to have the molecular weight 584. Hemin has a molecular weight 652 and 1 gm. of hemoglobin contains 3.35 mg. of iron. On the basis of these data, when 1 gm. of hemoglobin is destroyed there should result 34.9 mg. of bilirubin.

The blood hemoglobin level was determined following the method of Robsch¹¹ and blood volume by the brilliant vital red technique. Red blood cell counts were made using a Thoma diluting pipette and Neubauer counting chamber. In 2 dogs hemoglobin was determined as oxyhemoglobin and read in the Klett Summerson photoelectric colorimeter, and hematocrit cell values were estimated using Wintrobe hematocrit tubes.

Heinz corpuscles were studied after mixing 1 drop of blood with 1 drop of 0.5% brilliant cresyl blue in saline solution and were then counted in relation to the intact red blood cells. One thousand cells at least were observed.¹

TABLE 1.—HEMOGLOBIN DESTRUCTION AND BILE PIGMENT RECOVERY—BILE FISTULA.

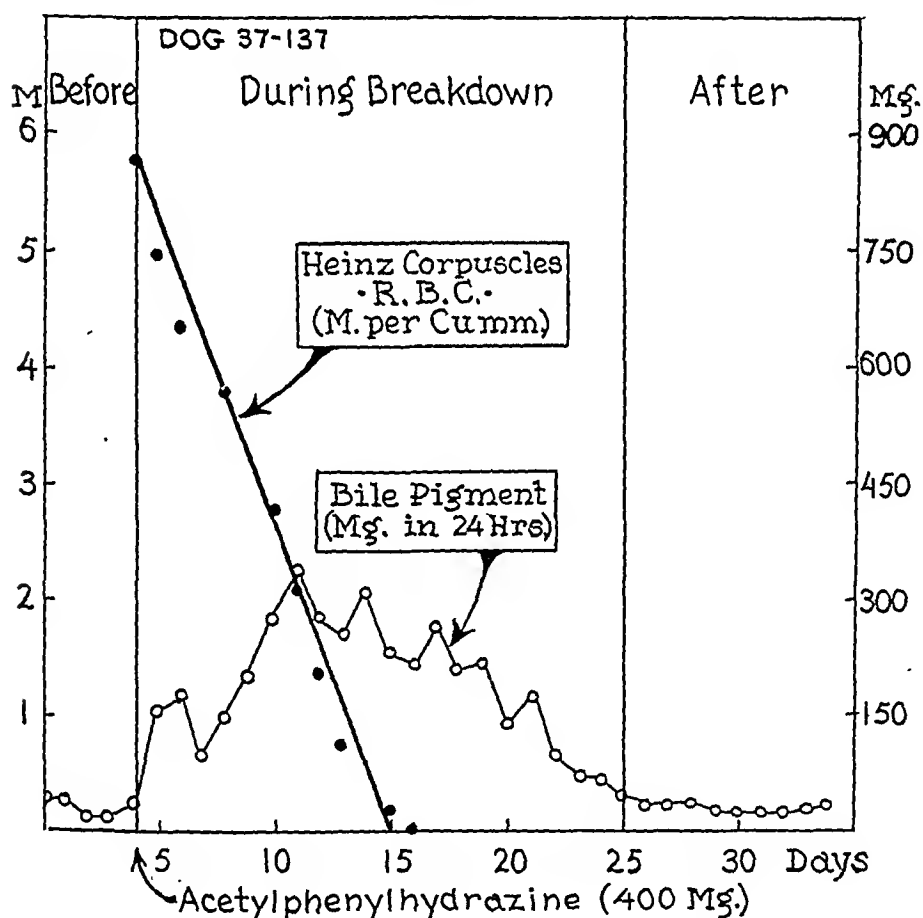
Dog (bile fistula)	31-271.	31-271.	34-211.	34-211.	34-212.	37-137.	40-248.
Body weight (kg.)	13	13	18	18	17	10	16
Hemoglobin (gm. 100 cc. blood)	17.9	15.5	16.2	16.6	17.3	13.6	13.6
Total blood volume (cc.)	1030	1030	1440	1440	1360	858	1131
Circulating hemoglobin (gm.)	185	160	232	239	235	117	154
Bilirubin equivalent of circulating Hb. (mg.)	6456	5584	8097	8341	8202	4083	5375
Acetylphenylhydrazine, injections and dose (mg.)	8 x 100	8 x 120	10 x 100 3 x 150	10 x 100	6 x 100	2 x 200	2 x 300
Before breakdown:							
Days of observation	36	23	15	15	7	20	26
Av. bilirubin output (mg. daily)	60	65	120	66	93	35	93
During breakdown:							
Days of observation	28	22	40	40	19	20	20
Total bilirubin output (mg.)	5798	5150	12,500	12,115	7196	3980	7296
After breakdown:							
Days of observation	36	9	15	14	15	10	10
Av. bilirubin output (mg. daily)	44	59	64	88	45	32	56
Total bilirubin output above control periods (mg.)	4342	3786	8820	9035	5885	3210	5806
Percentage recovery of bilirubin derived from circulating Hb.	67	68	100	108	72	79	108

Experimental Observations. Table 1 presents 7 instances of red blood cell breakdown in 5 dogs which varied in weight with blood volumes ranging from 858 to 1440 cc. and total circulating hemoglobin volume between 117 and 239 gm. The bilirubin equivalent of the circulating hemoglobin is readily obtained: 1 gm. hemoglobin = 34.9 mg. of bilirubin. The total amount of acetylphenylhydrazine varied from 400 to 1450 mg., as indicated in the table. Control levels of bile pigment were obtained by adequate control periods before and after administration of the drug. In order to obtain the amount of excess bile pigment resulting from the destruction of red cells, we have subtracted from the total amount of bile pigment eliminated during the breakdown period that amount corresponding to the average excreted in the fore and after control

periods. It might be argued that the lower figure should be used in all cases but we do not know the make-up of this basal bile pigment output. It is probable that some pigment is derived from muscle hemoglobin. Comparison of the excess bile pigment excreted with the theoretical amount that would result if all the circulating hemoglobin had been destroyed gives the percentage recovery. It ranges from 68% to 109%.

Dog 37-137 had had a similar blood destruction experiment performed just prior to the one that is tabulated and one notes the fore period level of bile pigment is low, 35 mg. as compared with 32 mg. in the after period. Dog 34-212 shows similar low bile pigment values in the fore period level in the second experiment when contrasted with the original bile pigment level in the first experiment. These lower than normal values are due to the fact that the dogs' circulating red cells following an anemia period were all new and therefore obsolescence was very low.

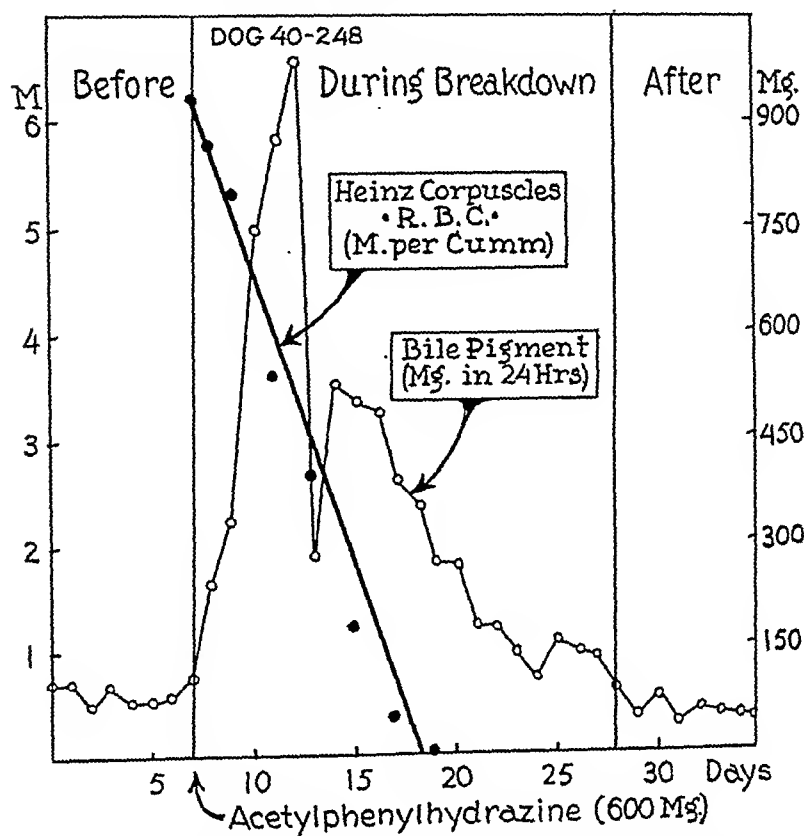
CHART 1.



In Charts 1 and 2 are plotted the daily bile pigment elimination and the rate of destruction of the red cells damaged by the drug during the breakdown period. It was observed that all red cells

injured by the hydrazine (red blood cells containing Heinz corpuscles) had disappeared from the circulation 12 days after the hydrazine was started. During the period of destruction the plasma

CHART 2.



was jaundiced and in both dogs excess bile pigment elimination was maintained for 8 more days after the disappearance from the circulation of the erythrocytes injured by the drug. This lag in elimination is due to the fact that the liver cannot handle the large excess of bile pigment formed daily and consequently it is retained in the blood and body tissues.

TABLE 2.—RED BLOOD CELL DESTRUCTION AND RECONSTRUCTION.

	Day of observation.		R. B. C. (mil. per c.mm.).		Hemoglobin (gm. 100 cc. blood).		Hematocrit (%).		Mean corpuscular volume (cubic micra).	
	37-137	40-248	37-137	40-248	37-137	40-248	37-137	40-248	37-137	40-248
Dog No.	0	0	5.8	6.2	13.6	13.6	43.5	40.5	75	65
Before breakdown .	8	8	3.2	3.4	7.4	7.4	26	26.5	81	75
Lowest anemia level	20	21	5.9	5.7	15.1	14.2	48	44	81	77
After breakdown .										

Table 2 presents the blood picture at the critical points of the experiments. From a relatively normal blood picture as shown before breakdown, the dogs have reached the lowest anemia level

observed 8 days after the first injection. On this day 85% of the injured cells had disappeared from the blood in Dog 37-137 and 78% in Dog 40-248. As these injured cells disappeared, new cells were appearing in great numbers sufficient to raise the blood count 400,000 to 500,000 per c.mm. daily. Consequently, the red cell levels did not drop below the levels indicated in the tables as loss of cells was compensated for by production of new cells.

Discussion. When hemoglobin was given by vein to an anemic bile fistula dog it was shown in this laboratory^{4,6} that new hemoglobin is produced in amounts equivalent to that injected; and, in addition, an excess of bile pigment appears in the urine which approximates 80% to 90% of the pigment radicle contained in the injected hemoglobin. The dog uses the iron and probably the globin of the injected hemoglobin and discards the pigment radicle. Obviously, the dog must be able readily to produce this pigment radicle.

When *hemoglobin* is *destroyed* in the dog (hydrazine), one could not safely assume that the response would be precisely the same as when hemoglobin is given by vein. The experiments above indicate that destroyed red cells do contribute hemoglobin or its split-products to the circulation which behaves as does the injected hemoglobin. Measurements cannot be as accurate because the amount of destroyed hemoglobin and red cells depends upon blood volume measurements which admittedly are subject to considerable variables and errors. However, the average values are significant and indicate that the expected amount of bile pigment is produced from the pigment radicle of the freed hemoglobin. Moreover, the new production of hemoglobin is very rapid and shows maximal activity ($60 \pm$ gm. hemoglobin per week) in spite of the fact that the diet of these dogs by itself is known to permit minimal hemoglobin production (2 to 4 gm. hemoglobin per week).

It does not seem desirable to discuss at length the limitations of blood volume measurements,^{3,13,15} but it is safe to say that the determination of red cell volume by the dye method and red cell hematocrit is too high. Therefore, less red cells than the calculated volume were actually destroyed, which brings the actual bile pigment figures very close to the theoretical return.

Polycythemia is frequently treated by phenylhydrazine and it must be obvious that hemoglobin destroyed in this fashion is at once available to form new hemoglobin for red cells. It would seem more logical to *remove* by bleeding the surplus red cells and limit as much as possible the intake of foods which favor the rebuilding of hemoglobin. In fact, this technique has been used successfully to treat polycythemia¹⁶ and with favorable response from the patients. Today these patients could at the same time make a significant contribution to blood banks.

Summary. When red cells are destroyed by acetylphenylhydrazine in the healthy bile fistula dog, we note a great output of bile

pigment which corresponds closely (88%) to the calculated amount which could be derived from the destroyed red cells and hemoglobin.

At the same time the dog produces almost maximal amounts of new hemoglobin and red cells, presumably utilizing the iron and perhaps globin from the destroyed hemoglobin. The diet does not contribute significantly to the new hemoglobin production.

New pigment radicles (pyrrol aggregates) appear to be readily formed by the dog under these and other conditions.

Acetylphenylhydrazine in the doses given destroys almost all of the mature red cells in the circulation. This type of injury produces Heinz corpuscles in all mature red cells.

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THE RELATION OF PERNICIOUS ANEMIA TO SOLAR RADIATION AND SKIN CANCER.

BY FRANK L. APPERLY, D.Sc., M.D.,

PROFESSOR OF PATHOLOGY, MEDICAL COLLEGE OF VIRGINIA, RICHMOND, VA.

IN 1934, J. H. Smith⁵ showed a significant relationship between relative lack of solar radiation and mortality from pernicious anemia in the United States prior to the introduction of the therapeutic use of liver. The relative intensities of solar radiation in the various states were represented by an "index," calculated from data directly observed in each state (actual amount of sunshine, angle of incidence of sun's rays and humidity). There are, however, several factors, the effects of which cannot be satisfactorily evaluated, *e. g.*, altitude, dust, and so on, together with other, but unknown, conditions. Further, no account was taken of possible variations of "sensitive-ness" depending on individual and racial differences, or on the effects

of other climatic conditions on the exposed populations. Although in most cases an excellent correlation was shown between the "solar radiation index" and pernicious anemia mortality, the calculated index in a number of states was obviously far too great.

It occurred to us that any relationship between pernicious anemia and solar radiation might be more accurately shown by an attempt to correlate this disease with some other human condition or disease

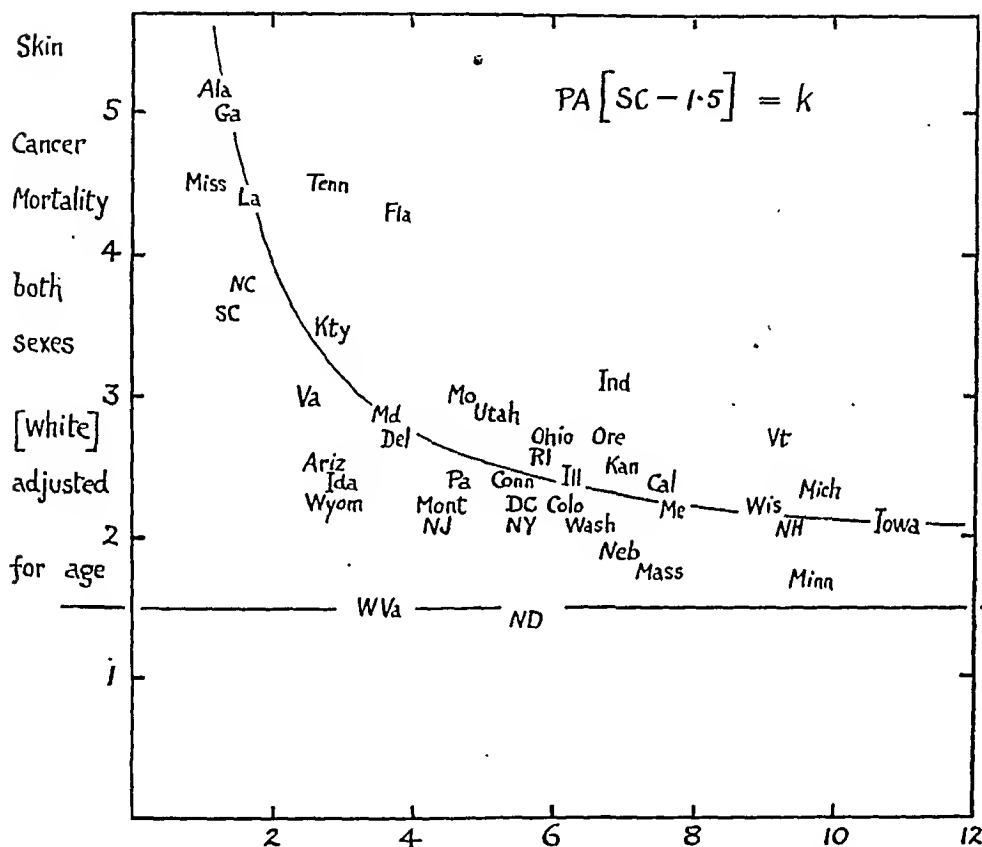


FIG. 1.—Pernicious anemia mortality rate (1921–1926) compared to skin cancer mortality rate in different states.

which was known to be related to sun exposure. In this way the difficulties of estimating both the "effective" solar radiation and the variations in human susceptibility and degree of exposure might be eliminated. For this purpose the incidence of skin cancer would seem to be a possibly more reliable instrument for measurement. In the absence of data concerning the total incidence of skin cancer, however, we have used the mortality figures.

In Figure 1 the pernicious anemia death rates for each state (average of the years 1921–1926) have been plotted against the skin cancer death rates. The graph shows that the relationship between these two diseases is much closer than that between pernicious anemia and Smith's calculated "radiation index." Thus, those states (Arizona, California, Colorado, Kansas, Iowa, Nebraska and

Utah) which showed the greatest discrepancies in Smith's graph fall very close to the median curve in Figure 1.

The total skin cancer mortality is, of course, made up not only of those caused by exposure to sunlight, but includes those of occupational and other origins. There is reason to believe that the latter accounts for about 1.5 per 100,000 population (Apperly¹). If this quantity (q) be deducted from the total skin cancer mortality ($S\ Ca$) then the shape of the curve shows that the relation of sun cancer ($S\ Ca - q$) to pernicious anemia mortality (PA) is such that

$$PA \times (S\ Ca - q) = \text{a constant, } K.$$

This strongly supports Smith's thesis that the incidence of pernicious anemia is related inversely to effective solar radiation.

The nature of this inverse relationship is unknown but some recent observations are suggestive. (a) Jacobson³ has shown a striking parallelism between the distribution of the argentaffin cells and the localization of the principle active against pernicious anemia in the walls of the stomach and gut, and that people with pernicious anemia have few or no argentaffin cells in these areas. These two facts certainly suggest some close relationship between the argentaffin cells and pernicious anemia. Jacobson has also shown that the argentaffin cells contain exocrine granules which are not only responsible for taking the silver stain but are in part made up of aromatic or benzene rings. (b) Benzene ring compounds are derived from tyrosine and similar aromatic amino-acids. Arnow² contends that the oxidation of tyrosine to dihydroxy-phenylalanine ("dopa") is brought about by ultraviolet light. With inadequate sunlight we would therefore expect some defect in the production of all of those substances which in turn are derived from "dopa."

Conclusion. When the mortality rates of pernicious anemia and skin cancer (corrected for other causes than exposure to sunlight) are correlated, it appears that the incidence of pernicious anemia is closely related inversely to effective solar radiation.

When we recall the close association of pernicious anemia with blond and prematurely gray-haired people, often of a eunuchoid type, and with diabetes,⁴ and that argentaffin granules, para-amino-benzoic acid, melanin, insulin and sex hormones are all composed partly of benzene or aromatic rings, there is a strong suggestion that these substances are dependent for their formation on an adequate production of dihydroxyphenylalanine through the agency of solar radiation. Whatever the ultimate explanation, the nature of these associations would seem to be well worth investigation on the lines suggested.

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THE TREATMENT OF POLYCYTHEMIA VERA WITH LEAD COMPOUNDS.*

BY ERNEST H. FALCONER, M.D., C.M.,

CLINICAL PROFESSOR OF MEDICINE, UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL,
SAN FRANCISCO, CALIF.

(From the Department of Medicine, University of California Medical School.)

STUDIES on patients with polycythemia vera reported in 1933^{1a,b} indicated that venesection in amounts up to 900 cc. of blood had no significant effect in raising the reticulocyte level. As I had investigated the effects of lead on the reticulocyte-stippled cell ratio in dogs and humans, it occurred to me that patients with polycythemia vera might be good subjects for observation concerning the effects of lead on the reticulocytes because their reticulocyte level appeared to be stable.

In 1934 and 1935 such experiments were carried out on 2 patients with polycythemia vera. Lead acetate was administered by mouth and the effects on the reticulocyte-stippled cell ratio were observed. When the red blood cells and hemoglobin had dropped to levels below normal, administration of lead was discontinued. There was an interval of 3 months in the one case and a longer period in the other during which the red blood cells and hemoglobin remained within normal limits and the patients felt a sense of well-being and freedom from symptoms which was rather surprising considering that lead had been absorbed over a period of several weeks. In 1935, as a consequence of interest aroused by these studies, I began treatment of polycythemia vera with lead compounds. I submit the following data which show the results of this treatment up to May 5, 1941.

Methods and Material. Blood counts were made with pipettes and counting chambers standardized according to the Bureau of Standards. Hemoglobin determinations were made by a standardized Sahli instrument (13.7 gm. = 100% hemoglobin). For the past 20 months we have used a Leitz-Mass photoelectric colorimeter for this purpose. The reticulocyte counts were made on dry films stained with cresyl blue, counterstained with Jenner-Giemsa stains. One thousand erythrocytes were counted on each film. Wintrobe tubes were used for the hematocrits. The blood volume determinations were carried out according to the Rowntree method as described by Haden.³ Platelet counts were done directly in the counting chamber using Rees and Ecker⁴ diluting fluids. Complete blood counts were made each time the patient reported, usually in the morning 2 to 3 hours after breakfast.

At the beginning of this study, lead acetate was administered by mouth in capsules of 0.3 gm.; later 0.2-gm. doses were used. Since July, 1939, the treatment has consisted of parenterally administered colloidal lead

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phosphate.* It is put up in 10-cc. ampoules; each 1 cc. contains from 3.7 to 3.8 mg. metallic lead. The usual dose was 10 cc. administered intravenously. No immediate reaction accompanied the injection but if the solution leaked out of the vein it was irritating to the tissues and caused some pain.

Clinical Material. Twelve patients with clinical and laboratory diagnosis of polycythemia vera were included in this study. Another somewhat questionable case (Case 8) was included that probably belongs in the group known as polycythemia hypertonica (Geisböck²). Of the series of 13 patients, 11 were treated with lead compounds orally, parenterally or by both routes. One (Case 12) was treated by intravenous injection of normal saline solution and 1 (Case 13) by small doses of acetylphenylhydrazine. These 2 patients served as controls.

The criteria employed for the diagnosis of polycythemia vera in these patients were as follows: A negative history for cardiac symptoms, for residence in high altitudes, for exposure to aniline dyes and carbon dioxide, for treatment with arsenic, liver extract, cobalt, or coal-tar derivatives (such as acetanilid); an increase of red blood cells above 6 million and of hemoglobin above 110%; a packed-cell volume (hematocrit) above 45% to 47%; an increased blood volume; presence of acrocyanosis, capillary engorgement and enlargement of spleen and liver; absence of a cardiac lesion or cardiovascular disease producing cyanosis, circulatory stasis and erythrocytosis.

Case Abstracts. CASE 1.—(Chart 1.) This patient, a woman of 65, was first seen in 1934 when her red blood cells were 7.70 million per c.mm.

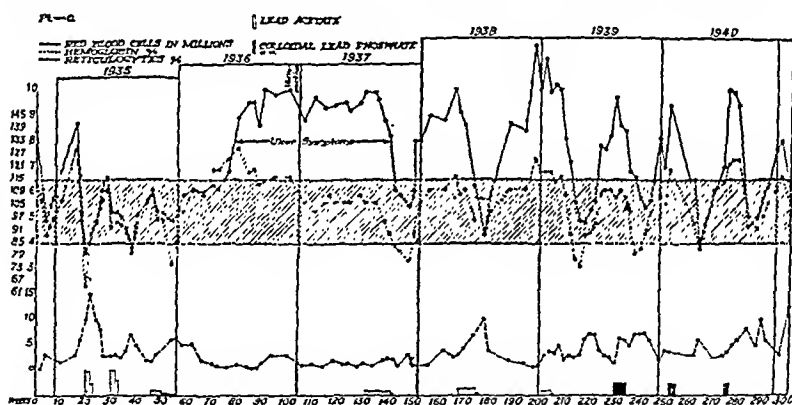


CHART 1.—Case 1. Blood cell levels during lead treatment. The shaded zone represents a theoretical normal range of red blood cells and hemoglobin for patients with polycythemia vera.

and her hemoglobin 140%. She had a history of gastric ulcer for 1 year. The diagnosis was proved by Roentgen examination; treatment by an ulcer regimen and phenylhydrazine was advised. During 1934 the gastric ulcer was reported healed by Roentgen examination and the patient received phenylhydrazine at intervals for the polycythemic state. On January 31, 1935, she was placed directly under my care. On March 4, 1935, her red blood cells were 7.54 million; hemoglobin 120%. Treatment with lead acetate was begun in doses of 0.3 gm. once daily by mouth. During the following year, to December 30, 1935, a total of 20 gm. lead acetate was administered *per os* at intervals (see Chart 1). For an interval of 3 months

* This preparation is made by the Crookes Laboratory, New York City.

no lead compounds were given and the red blood cells and hemoglobin remained within normal limits. (Such periods are hereafter referred to as remissions.) For the next year and 7 months, until July 26, 1937, no lead was administered; a remission of 5 months occurred. During the next 26 months, to August 7, 1939, the patient received a total of 19 gm. lead acetate by mouth (see Chart 1) and had three remissions of $6\frac{1}{2}$, 4 and 4 months respectively. From August 7, 1939, to May 5, 1941, 108 cc. (0.4 gm.) colloidal lead phosphate were administered intravenously and three remissions occurred, 4.6, 5.3 and 4 months respectively. For 2 years the patient has been free of gastro-intestinal symptoms, has had occasional arthritic pains (long-standing generalized arthritis) but has been able to do her housework and to nurse an invalid husband which she was not able to do for 4 years previously. During the first year of lead therapy we deliberately induced a toxic episode in order to study the effects of lead on her blood cells and did not have in mind treatment of her polycythemia. Lead compounds were used in lesser amounts for the treatment, which followed the toxic episode.

CASE 2.—(Chart 2.) A man of 54 had a history of his eyes being "red and bloodshot" and of generalized arthritic pains for 8 years. In 1934 a

Pt.—W.

— RED BLOOD CELLS IN MILLIONS
 HEMOGLOBIN %
 - - - - - RETICULOCYTES %
 ▮ LEAD ACETATE

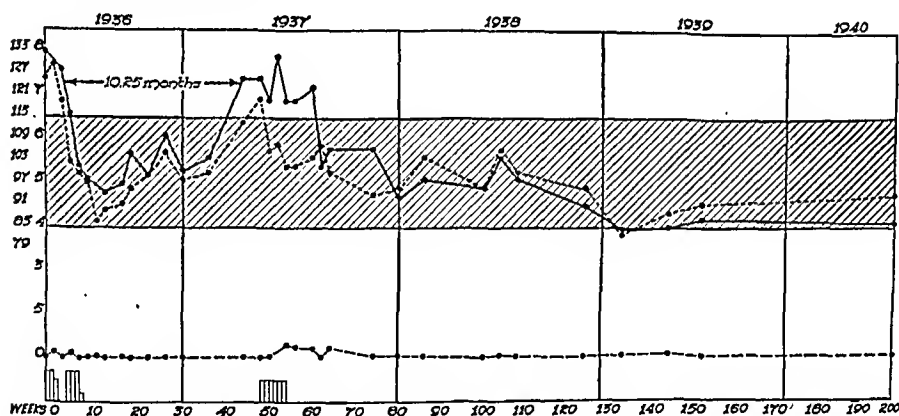


CHART 2.—Case 2. Blood cell levels during lead treatment. Note the comparatively small amount of lead administered in this case.

diagnosis of polycythemia vera was made and treatment with phenylhydrazine and venesection was instituted. His blood level did not remain at a normal level under this treatment and he complained of dizziness, weakness and dyspnea. On April 22, 1936, the red blood cells were 8 million per c.mm.; hemoglobin, 128%; leukocytes, 9400; and packed cell volume, 65%. Beginning April 29, 1936, the patient received orally 0.3 gm. lead acetate twice daily for 6 days; thereupon the dose was administered once daily. During 1936 he received a total of 7 gm. lead acetate by mouth. During 1937 he received a total of 3 gm. Since August 28, 1937, no lead has been administered. A remission occurred which lasted until June 15, 1940. Since that date the patient has not been located.

CASE 3.—A woman of 61 had a history of polycythemia vera for 27 years and had been under my observation for 25 years. In 1916 her red blood cells were 10.64 million; hemoglobin, 128% (Fleischl); leukocytes, 9800; and viscosity (Hess), 7.7 (normal 4.5). She was treated as follows: venesection, 1915; benzol by mouth combined with radiation over the spleen,⁵

1916, was followed by a remission of 11 years; Roentgen ray treatment over the spleen, 1928; phenylhydrazine, 1929 to 1930; venesection, 1931; Roentgen ray treatment over spleen and long bones, 1932; acetylphenylhydrazine, 1932 to 1933; lead acetate by mouth, 1935. On July 27, 1934, the red blood cells were 7.16 million; hemoglobin, 118%; and leukocytes, 11,200. During the next 17 months, until December, 1935, a total of 12 gm. lead acetate was administered orally. At one time the red blood cells dropped to 3.27 million, hemoglobin to 56% and leukocytes to 9300 per c.mm. The effects of the lead on the cells of the blood were investigated during this period and treatment was not under consideration. Since December 31, 1935, no lead has been administered. The blood count has not risen above normal limits and no untoward symptoms have appeared. The blood count on May 5, 1941, was: red blood cells, 4.58 million; hemoglobin, 96%. Packed cell volume was 41 cc. %. During the five years immediately preceding the administration of lead, the longest period of remission was 8 months.

The large amounts of lead administered to this patient should not be used therapeutically, as she experienced a severe toxic episode. Whether or not the long remission following administration of lead acetate was due to lead is open to question. It may have been coincidental. The patient had a long remission of 11 years following an entirely different type of treatment during the early course of her disease.⁵

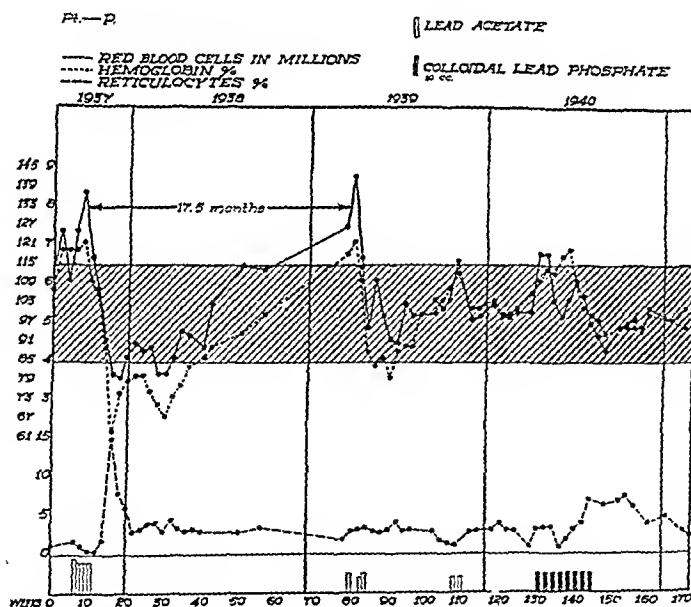


CHART 3.—Case 4. Blood cell levels during lead treatment. The low hemoglobin of 61% occurred following sufficient absorption of lead acetate to cause a toxic episode.

CASE 4.—(Chart 3.) An obese man of 45 (206 pounds) was examined at the San Francisco Hospital in June, 1936, and the diagnosis of polycythemia vera was made. He tolerated phenylhydrazine poorly and at one time during 1936 it became necessary to give him a blood transfusion. On September 22, 1937, the red blood cells were 6.82 million; hemoglobin, 120%; and leukocytes, 6200 per c.mm. During 1937, he received a total of 10.5 gm. lead acetate by mouth. This treatment was followed by a

remission which lasted throughout 1938. During 1939 the patient received 5.4 gm. lead acetate by mouth. During 1940 he received three 10-cc. doses of colloidal lead phosphate intravenously (see Chart 3 for remission). On April 30, 1940, the hematocrit (packed cell volume) was 60. Blood volume was 67.61 cc. per kilo of body weight.*

CASE 5.—(Chart 4.) This Jewish woman of 63 had a high red blood cell count and increased hemoglobin for 5 years. In 1937 a definite diagnosis of polycythemia vera was made. She had a long-standing thrombophlebitis

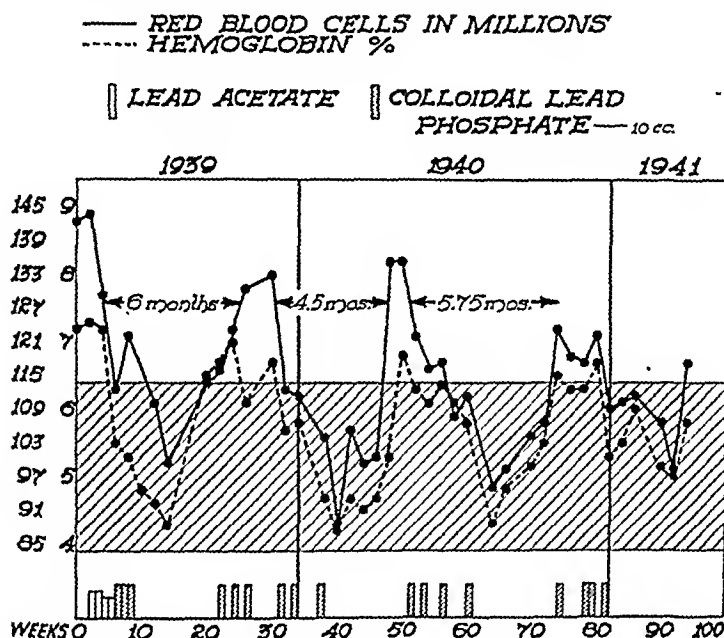


CHART 4.—Case 5. Blood cell levels during lead treatment. This patient had a moderately severe and persistent polycythemia.

of the right lower extremity and for 10 years much discomfort from arthritis of shoulders, hands, knees and feet. She had moderate hypertension and displayed great anxiety over her condition. For 14 days, beginning May 6, 1939, she received 0.2 gm. lead acetate by mouth, a total of 2.8 gm. During the next week she received 16 cc. colloidal lead phosphate intravenously (66.8 mg. metallic lead). A remission of 4.6 months followed. In October, November and December, 1939, she received 40 cc. colloidal lead phosphate. This treatment was followed by a remission of 7 months. During 1940 she received a total of 50 cc. colloidal lead phosphate intravenously (190 mg.). Before beginning the lead treatment, she had been troubled much with nausea and what she called "biliousness." Under this regimen, which I regard as conservative, she has never been troubled with toxic reactions, such as headache, nausea, vomiting, abdominal pain and muscular weakness. She had increased arthritic pain and edema of the lower extremities (see Chart 5 for blood levels). She worked steadily as a teacher during her treatment. On May 8, 1940, the packed cell volume was 62 cc. %; blood volume, 68.5 cc. per kilo of body weight.

CASE 6.—(Chart 5.) A Jewish man of 52 came under observation on July 22, 1939. His blood count was as follows: red cells, 8.15 million; hemoglobin, 130%; white blood cells, 8100 and packed cell volume 64 cc. %. "Redness of the eyes" and fullness of the head had persisted for 1½ years, since January, 1938. A diagnosis of polycythemia vera was made in New

* Normal blood volume for men, 65 cc. per kilo of body weight; for women, 66 cc.

York City and treatment with acetylphenylhydrazine was instituted in June, 1939. From August 14, 1939, to November 19, 1941, he received a total of 80 cc. (0.29 gm.) colloidal lead phosphate intravenously. On May 15, 1939, the packed cell volume was 52% and the blood volume 66.6 cc. per kilo of body weight. The red blood cell and hemoglobin levels (Chart 5) were uniformly at the higher limits of normal, but the patient was free of symptoms and worked steadily in his profession (cantor in a synagogue). No toxic symptoms have resulted from lead administration.

CASE 7.—(Chart 5.) This patient, aged 45, who was cyanotic and had a "beefy," red face and acrocyanosis, was referred from the department of dermatology where she had been under treatment for dermatitis

Pt.—Gr.

Pt.—R.

— RED BLOOD CELLS IN MILLIONS

..... HEMOGLOBIN %

| COLLOIDAL LEAD PHOSPHATE

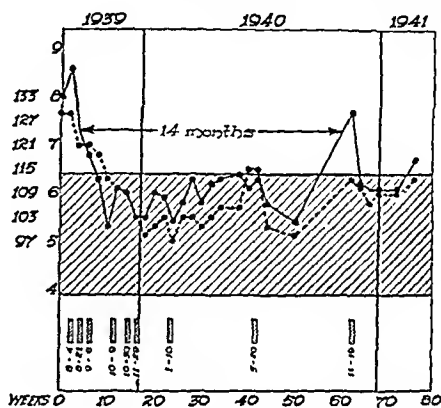
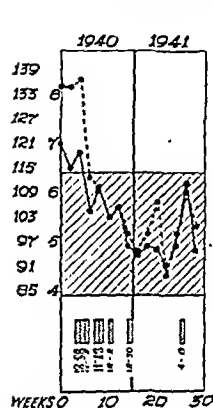


CHART 5.—Cases 6 and 7. Blood cell levels during lead treatment. Only one form of lead was used in these 2 cases—colloidal lead phosphate.

of the right lower leg "on a circulatory basis." Red blood cells were 7.1 million; hemoglobin, 130%; leukocytes, 12,300; packed cell volume, 66; blood volume 93.2 cc. per kilo. From October 26 to December 2, 1940, she received by intravenous injection 50 cc. colloidal lead phosphate (0.18 gm.) (Chart 5). No untoward symptoms have occurred.

CASE 8.—(Chart 6.) A man of 64 had borderline polycythemia. The liver was enlarged. The spleen was not palpable. Red blood cells were 5.6 million; hemoglobin, 120%; leukocytes, 13,800. The diagnosis was made principally on basis of a packed cell volume of 52 cc. % and blood volume of 70.4 cc. per kilo of body weight. During a 2-week period, he received a total of 30 cc. (101 mg.) colloidal lead phosphate intravenously. His symptoms of dyspnea, headache and fatigue disappeared.

CASES 9, 10 and 11.—(Chart 7.) These patients, a woman of 51 and 2 men of 58 and 54 respectively, are examples of seriously disabling polycythemia vera with complications due to thrombosis. The woman had attacks of severe abdominal pain with hemorrhages from the gastro-intestinal tract but no evidence by Roentgen examination of a gastro-intestinal lesion. The 58-year-old man had a diagnosis of thrombosis of the pulmonary artery. The third patient had extensive thrombophlebitis of the lower extremities with varicose ulcers.

In all 3 patients administration of lead in the form of colloidal lead phosphate has caused prompt and severe toxic reactions, such as weakness, generalized pain, abdominal pain and headache. It might be pointed out

that these patients had not tolerated any other type of treatment without being "much upset," although they had tolerated venesection better than phenylhydrazine or Roentgen ray treatment.

CASE 12.—(Chart 6.) A Jewish refugee of 52, with family history of polycythemia in the father, was much upset emotionally and mentally

Pt.—M.

Pt.—F.

— RED BLOOD CELLS IN MILLIONS
 HEMOGLOBIN %

COLLOIDAL LEAD PHOSPHATE
 10 cc.

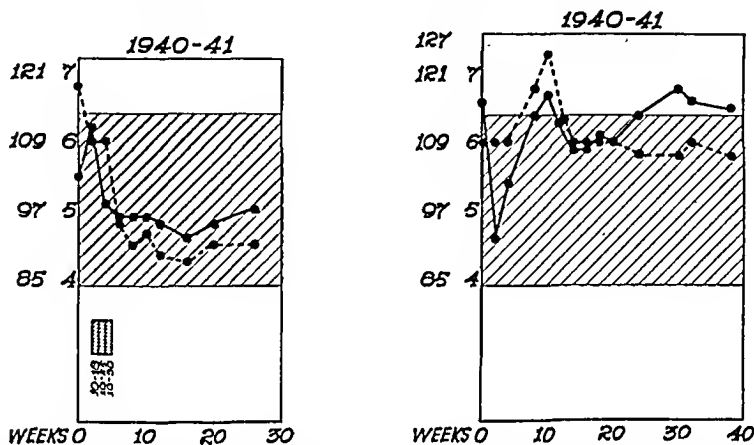


CHART 6.—Cases 8 and 12. Blood cell levels without lead treatment. Patient F (Case 12) received normal saline, 20 cc. intravenously, at intervals of 3 weeks.

due to recent experiences in Europe. He had a variety of symptoms following any kind of treatment attempted. We decided to give him 20 cc. normal saline intravenously every 3 weeks and to employ him as a control for the lead-treated patients (see Chart 6 for results).

Pt.—S.

Pt.—F

Pt.—J

— RED BLOOD CELLS IN MILLIONS
 HEMOGLOBIN %

COLLOIDAL LEAD PHOSPHATE

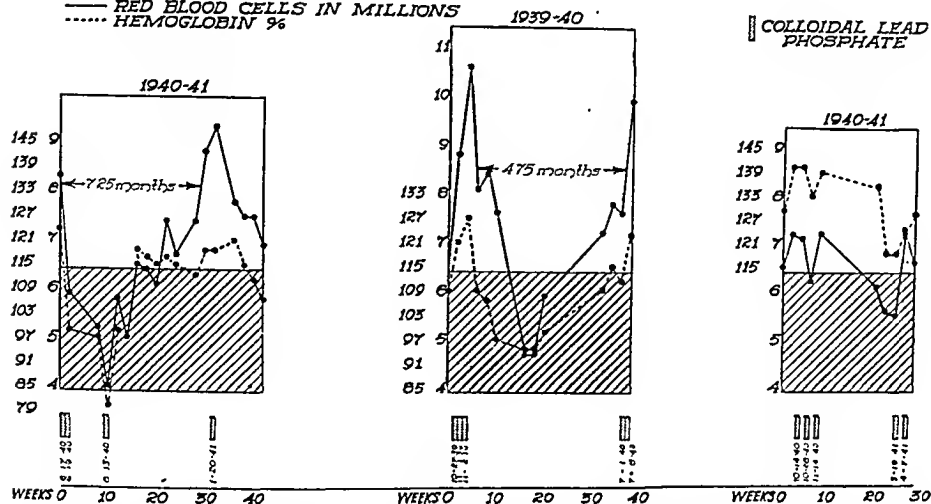


CHART 7.—Cases 9, 10 and 11. Blood cell levels during lead treatment. Patient S (Case 9) had gastro-intestinal hemorrhages following intravenous administration of lead; hemoglobin fell to 79%.

CASE 13.—(Chart 8.) A retired school teacher of 63 was referred to me on July 6, 1937, by Dr. C. T. Stone of Galveston, Texas, who had made a diagnosis of polycythemia vera in 1929 and had placed the patient on intermittent small doses of acetylphenylhydrazine, 0.1 gm. once every 5 to 7 days. This treatment was continued with good results until July, 1937. Since that time the polycythemic state has been under control and the periods of intermission have been lengthened (Chart 8). On August 22, 1940, her red blood cells were 5.4 million; hemoglobin, 100%; leukocytes, 12,200. The patient was admitted to a hospital and 4 teeth, which had been loose and the site of extensive paradentosis, were extracted by a competent dental surgeon. Extensive hemorrhagic oozing followed and

Pt—Ga

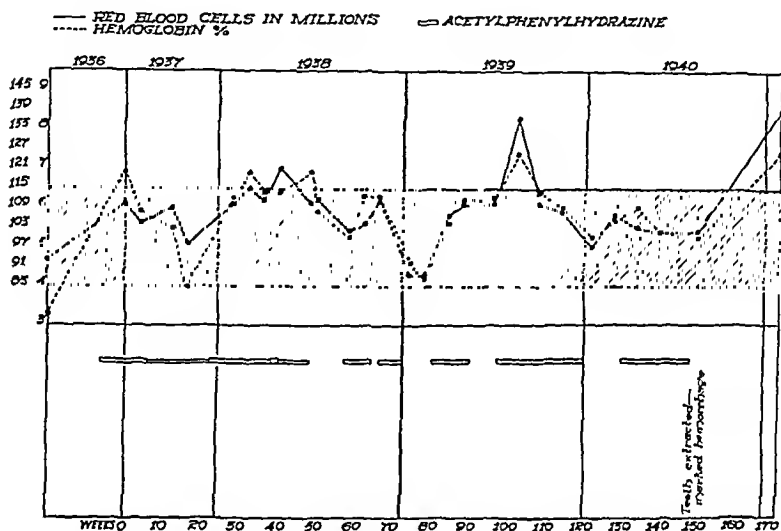


CHART 8.—Case 13. Blood cell levels without lead treatment. Acetylphenylhydrazine in doses of 0.1 gm. was given once per week or less often.

could not be controlled. The tissues of the floor of the buccal cavity became infiltrated with blood and infection supervened complicated by bronchopneumonia. After 4 months of hospitalization the patient slowly recovered. On February 15, 1941, the red blood cells were 8.5 million; hemoglobin, 126%; leukocytes, 21,200. This patient is included in the series as a control case for the lead-treated patients.

Discussion. Analysis of the foregoing data indicates that the response of patients with polycythemia to lead therapy varies and that in certain patients this type of therapy is contraindicated. In Cases 9, 10 and 11, for example, lead therapy was poorly tolerated. These patients showed extensive thrombotic lesions; 1 had widespread thrombophlebitis of the superficial veins of the upper and lower extremities. They also reacted unfavorably to other types of therapy, such as phenylhydrazine and Roentgen. Venesection upset them less than the other therapeutic measures. Cases 3, 12 and 13 represent mild types of the disease in which remissions were induced easily by any of the generally accepted methods of

treatment. In evaluating any type of therapy, including colloidal lead, the natural history of the disease must be taken into consideration, particularly the fact that it is characterized by all grades of severity. Probably no one standardized type of therapy would prove uniformly successful. This report is presented because the material contains important implications as to the factors responsible for excessive formation of hemoglobin and red blood cells.

It has frequently been demonstrated that porphyrins appear in the urine during absorption of lead in man. It was found in 3 of our patients at varying periods after administration of lead had been discontinued. Watson⁵ demonstrated that Coproporphyrin III appears in the urine of patients with lead intoxication. This substance apparently occurs when the bone marrow is unable to synthesize hemoglobin properly and is not due to an increased rate of hemoglobin destruction. Inasmuch as patients with polycythemia apparently synthesize hemoglobin too readily, a substance which checks this tendency, such as lead, is a useful agent if properly controlled. Three of our patients who have been under treatment with lead for a period of 5 years have shown no deleterious effects as far as I have been able to ascertain.

The results obtained in this series were far more satisfactory than was considered possible at the beginning of the treatment. Nevertheless, I wish to emphasize the dangers of lead ingestion and of the intravenous use of lead compounds. The administration of lead acetate by mouth is rather unsatisfactory because one does not know how much lead the patient is absorbing and because cumulative effects may not be evident until a toxic episode occurs. Intravenous use of lead may damage the liver, the central nervous system or the peripheral nerves. Arthralgia is a common symptom after administration of lead and was most pronounced in those patients who had an abnormal amount of uric acid in the blood. The uric acid content per 100 cc. of blood was as follows: Case 1, 6.8 mg.; Case 4, 5 mg.; Case 5, 4 mg.; Case 6, 4 mg.; Case 7, 4.6 mg.; and Case 9, 8 mg. These are single observations after initiation of lead therapy, so that the findings can be interpreted as only suggestive of what well-controlled studies might reveal.

The reticulocytes were recorded in the counts of all patients except the 2 controls. Charts 1, 2 and 3 show how they increased as the red cell count dropped. The rise began as soon as the red blood cells had decreased appreciably. Intravenous administration of colloidal lead phosphate appeared to cause a rise of reticulocytes sooner than lead administered *per os*. This is due to the fact that colloidal lead phosphate begins to destroy the red blood cells immediately after it has been administered.

Summary. Eleven patients with polycythemia vera were treated with lead compounds orally and intravenously over periods of time varying approximately from 1 to 5 years. Nine of these patients

were relatively free of symptoms during treatment and were able to continue their work. Two patients with complicating thromboses were chronic invalids and unable to work. In cases of complicating thromboses, of which 3 occurred in this series, treatment with lead is contraindicated. Up to the present time no permanent or serious toxic effects have occurred in any of the 11 patients treated. No deaths have occurred in the series during the past 5 years. One patient has disappeared from observation.

Six of the 11 patients who were treated with lead had previously received phenylhydrazine. They regarded this drug as more toxic and disabling than lead and were unwilling to submit to further treatment with it. We do not, however, have data as to the amount of the drug and the intervals at which it was administered.

In selected cases of polycythemia vera, colloidal lead phosphate, administered intravenously in doses of 10 cc. each, appears to be efficient in controlling the symptoms and in reducing the blood level. The dangers of this preparation are real and it should not be used unless the patients can be kept under careful supervision.

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THE TREATMENT OF THE TUBERCULOUS WOMAN DURING PREGNANCY.*

BY E. S. MARIETTE, M.D., F.A.C.P., F.A.C.H.A.,

SUPERINTENDENT AND MEDICAL DIRECTOR, GLEN LAKE SANATORIUM; CLINICAL ASSISTANT PROFESSOR OF MEDICINE, MEDICAL SCHOOL, UNIVERSITY OF MINNESOTA,

LEONARD M. LARSON, M.D.,

SENIOR RESIDENT PHYSICIAN, GLEN LAKE SANATORIUM; ASSISTANT IN MEDICINE, MEDICAL SCHOOL, UNIVERSITY OF MINNESOTA,

AND

J. C. LITZENBERG, M.D., F.A.C.S.,

EMERITUS PROFESSOR OF GYNECOLOGY AND OBSTETRICS, MEDICAL SCHOOL, UNIVERSITY OF MINNESOTA.

MAN's ideas of the effect of pregnancy upon the tuberculous process have varied with his understanding of the nature of the mechanism of recovery from that disease. Because of the general improvement in health which so frequently accompanies early

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pregnancy, writers formerly advised pregnancy as a preventive or curative measure. Unfortunately, under the then accepted methods of treatment this improvement was more apparent than real and was due to the stimulating effect of pregnancy upon the frame and figure of the woman rather than to any improvement in the tuberculous lesion. When the stimulating effect of pregnancy was removed, the disease spread very rapidly. Recognition of this fact caused the pendulum to swing to the other extreme and a therapeutic abortion was advised in all cases where the pregnancy was discovered before the fifth month.

With the development of the Roentgen ray, the sanatorium movement and the appreciation of the importance of rest, both general and localized, in the treatment of tuberculosis, has come a better understanding of tuberculosis and the mechanism of recovery. As a result, the emphasis in the treatment has gradually shifted from those measures which will affect the frame and figure to a direct attempt to control the tuberculous process itself.

This change in the emphasis of treatment caused us in 1921 to question the necessity of aborting the pregnant tuberculous woman just because of the tuberculosis. We noticed that most of the reports of the disastrous effects of pregnancy upon the tuberculous process came from obstetricians whose opinion must have been based largely upon the difference in the results of caring for the normal pregnant woman and the tuberculous pregnant woman. In arriving at their conclusions they apparently overlooked the fact that the tuberculous woman of child-bearing age has a much higher death rate than the non-tuberculous woman of the same age even though pregnancy does not exist. Apparently their conclusions were based on the improvement in the frame and figure which took place during pregnancy without improvement in the lungs only to be followed by a relapse later.

In studying this problem we recognized the self-evident fact that pregnancy in itself is a physiologic process for which woman was created and which normally is not harmful. Tuberculosis on the other hand is an infectious disease which annually kills thousands of women of child-bearing age even though pregnancy does not exist. Therefore, we felt that a study of the tuberculous women, both pregnant and non-pregnant, would throw some light on the effect of pregnancy upon the tuberculous process. We thought perhaps if the main effort of therapy was directed against the diseased process rather than against the normal physiologic process, the tuberculous pregnant woman could go to full term without interfering with her recovery from tuberculosis. If so it would bring happiness to many families who desired children but who are afraid to have them because of tuberculosis.

With that premise in mind we have divided our tuberculous patients into two groups, those with active tuberculosis and those

with chronic so-called "arrested" tuberculosis. The treatment of the two groups, of course, is different. The woman with active tuberculosis should have plenty of bed rest and such additional methods of treatment as pneumothorax and other forms of collapse therapy which would be used if pregnancy were not present. This is particularly true following labor when more intensive treatment may be indicated to prevent a spread of the disease when the stimulating effect of pregnancy is removed. We also realized that the pregnancy itself should receive just as careful if not more careful attention and consideration than it would receive in the absence of tuberculosis. Furthermore, should any condition other than tuberculosis be found which would warrant a therapeutic abortion, then, of course, it should be done even though tuberculosis is present.

The patient with tuberculosis who becomes pregnant after leaving the sanatorium should receive more careful prenatal care than if tuberculosis did not exist. Many of this group return to the sanatorium for care during the latter months of pregnancy. The exact treatment these women receive varies with the individual case and condition. In general, however, we keep them in bed, except for bathroom privileges, for the last 2 or 3 months prior to delivery and on strict bed rest for a month or 6 weeks after delivery. They are then allowed to gradually get up and to start exercise and are discharged in perhaps another 6 weeks. Of course they are not permitted to nurse their babies who are separated from them at birth and kept in a special ward planned for that purpose in the preventorium. In this way the woman receives adequate treatment for her tuberculosis and her pregnancy and the child receives 2 or 3 months of nursery care before being sent home with the mother.

With the above general premise in mind we have found it necessary to advise abortion in only one sanatorium case since 1921. As this policy represented quite a departure from the accepted treatment of the tuberculous woman during pregnancy, we watched our first few cases with considerable anxiety. However, we are glad to state that the results in our series of such cases extending over a 19-year period, seems to bear out our original presumption.

From September, 1921, to December, 1940, inclusive, we have had an opportunity to follow 8 premature deliveries in 8 tuberculous women and 96 full-term pregnancies in 86 tuberculous women. The age of the women in both of these groups was 18 to 39 years inclusive. This study includes women who were pregnant on admission to the sanatorium, who became pregnant while on leave from the institution or after discharge.

The 8 premature deliveries are analyzed on Tables 1, 2 and 3. According to these tables, 6 of the 8 were far advanced and 4 of them died within 2 weeks to 8 months after delivery. From a study of Table 2, it is apparent that all 4 would have died from tuberculosis irrespective of whether or not they were pregnant. The one

far-advanced case who was regarded as unimproved at time of discharge was transferred to another hospital 8 months after delivery. She died $4\frac{1}{2}$ years later. I question just how much pregnancy can be accepted as having contributed to a death which occurred that long after delivery. The other far-advanced case who was thought to have a questionable prognosis on admission was discharged as improved $1\frac{1}{2}$ months after delivery. Now, 8 years after her discharge, she is alive and well and during this interval has had one normal pregnancy.

TABLE 1.—CONDITION ON DISCHARGE OF PREMATURE LABOR CASES DELIVERED AT SANATORIUM (17-YEAR PERIOD).

Stage of disease on admission.	Condition on discharge.				
	Quiescent.	Improved.	Unimproved.	Dead.	Total.
Far advanced	1	1	4	6
Moderately advanced	1*	1
Extrapulmonary	1	1
Total	2	1	1	4	8

* Full-term delivery 3 years subsequently.

TABLE 2.—FURTHER DATA ON PREMATURE LABOR CASES DELIVERED AT SANATORIUM.

Admission diagnosis and stage of disease.	Age of mother at delivery.	Period of gestation.	Interval between delivery and discharge.	Prognosis or condition discharge.	Remarks.
Pott's disease	30	6½ mos.	1½ yrs.	Favorable	Well 10 yrs. later; has had 2 normal preg. since dis.
M.A.	31	7 mos.	6 mos.	Favorable	Well 13½ yrs. later; 1 normal preg.
F.A.	28	7 mos.	1½ mos.	Questionable	Well 8 yrs. later; 1 normal preg. since.
F.A.	27	6 mos.	8 mos.	Unfavorable	Died 4½ yrs. post-san.
F.A.	31	8 mos.	8 mos.	Dead	Cause: pul. chr. tbc.; tbc. of spine and perit.
F.A.	32	6½ mos.	14 days	Dead	Cause: pul. chr. tbc.; laryng. tbc.
F.A.	38	6½ mos.	3 mos., 20 days	Dead	Cause: pul. chr. tbc.; tbc. laryngitis; tbc. enteritis.
F.A.b.	21	7½ mos.	23 days	Dead	Cause: pul. chr. tbc.; tbc. generalized.

TABLE 3.—PREMATURE LABOR CASES. CORRELATION OF CAUSE OF DISCHARGE WITH STAGE OF DISEASE ON ADMISSION.

Stage of disease on admission.	Discharge condition.	Cause of discharge.				
		Acq.	Trans.	Ag. adv.	Dead.	Total.
Far advanced	Improved	..	1	1
	Unimproved	..	1	1
	Dead	4	4
Mod. advanced	Quiescent	1	..	1
Extrapulmonary	Quiescent	1	1
Total		1	2	1	4	8

There was one moderately advanced case who was discharged against advice 6 months after delivery. She was regarded as quiescent on discharge and is alive and well $13\frac{1}{2}$ years later. She also

had a normal full-term delivery at the sanatorium $3\frac{1}{2}$ years after her premature delivery and so is included in that group also. Because of duplications like this the total of the women in the various groups exceeds the number of women in the study.

The one case of extrapulmonary tuberculosis was thought to be quiescent when she was given an "acquiesced to discharge" $1\frac{1}{2}$ years after delivery. She is alive and well 10 years later and has had 2 normal pregnancies since her discharge.

Eight children were born of these 8 premature deliveries. One weighed 7 pounds at birth. She was born in the eighth month of gestation and while her mother died 8 months after delivery the child is now almost 9 years old and appears to be perfectly healthy. One was delivered 23 days before her mother's death in the $7\frac{1}{2}$ month of gestation, is now about a year old and seems to be perfectly healthy. The other 6 were born in the seventh month or less of gestation and all died within 1 hour to 16 days after delivery.

Prior to the establishment of our obstetrical department in 1924 the pregnant women were transferred to a general hospital for delivery. However, from 1924 to 1940, inclusive, 64 women with full-term pregnancies were delivered at the sanatorium. These are analyzed in Tables 4 to 7, inclusive.

TABLE 4.—RESULTS OF FULL-TERM PREGNANCIES DELIVERED AT SANATORIUM. FIRST DISCHARGE FOLLOWING DELIVERY (17-YEAR PERIOD, ENDING 1941).

	No. of deliveries per patient.	Mothers.				Total newborn.
		Still in hosp.	Disch. alive.	Disch. dead.	Total.	
59 patients (single birth)	1	6	48	5	59	59
2 patients (twins)	1	..	2	..	2	4
2 patients (2 single births each)	2	..	2	..	2	4
1 patient (3 single births)	3	..	1	..	1	3
Total	—	6	53	5	64	70

TABLE 5.—SIXTY-FOUR FULL-TERM PREGNANCIES DELIVERED AT SANATORIUM (1924-1940, INCLUSIVE).

	First admission.	Second admission.	Third admission.
Total	46	13	5
Dead on discharge:			
Number	5	0	0
Per cent	10.9	0	0

All discharges during same period, 18 to 39 years of age, 2230.

Dead on discharge, 559 (25%).

Six of the group are still hospitalized, 53 were discharged alive while 5 (7.8%) were dead at time of discharge (Table 4). This is a very low death rate when compared with the 20.45% of deaths for all women 15 to 39 years of age who were discharged during the same period.

Forty-six of this group (Table 5) were delivered during their first admission to the sanatorium. Of this group, 5 (10.9%) were dead at time of discharge in contrast to 559 (25%) of the 2230 women in the same age group who were discharged from the sanatorium for the first time during the same period.

Table 6 correlates the condition on discharge with the stage of disease on admission, and it is interesting to note that all of the 5 deaths in this series occurred in the far-advanced group.

TABLE 6.—FULL-TERM PREGNANCIES. CORRELATION OF CONDITION ON DISCHARGE WITH STAGE OF DISEASE ON ADMISSION (17-YEAR PERIOD).

	Stage of disease on admission.				Total.
	Far advanced.	Moderately advanced.	Minimal.	Stage undetermined.	
Condition on discharge:					
Inactive	1	1	2
Arrested	7	3	4*	2	16
Apparently arrested	1	1	..	2
Quiescent	6	5	11
Improved	9	9	3	..	21
Unimproved	1	3	4
Dead	5	5
Total	29	22	8	2	61†
Still in house	1	3	2	..	6
Grand total	30	25	10	2	67*

* Includes 1 non-clinical.

† Three mothers in this group are counted twice because they had more than one discharge following a pregnancy.

Table 7 considers the interval between the time of delivery and death for the full-term pregnancy group. This includes those who died in the sanatorium following delivery and those who died later. According to this table, 14 (21.8%) of the group are now dead. However, 2 (14.4%) of the 14 were due to non-tuberculous causes.

TABLE 7.—INTERVAL BETWEEN DELIVERY AND DEATH. FULL-TERM PREGNANCIES DELIVERED AT SANATORIUM (17-YEAR PERIOD).

	Stage of disease on admission.		Total.
	Far advanced.	Moderate advanced.	
Year interval between delivery and death:			
0 to 1	4	..	4
1 to 2	1	..	1
3 to 4	1	1
4 to 5	3*	..	3
5 to 6	1†	1
6 to 7	1	1	2
Over 12	2	..	2
Total	11	3	14

* Including post-san. Cardiac death.

† Including post-san. Death due to cause other than tuberculosis.

Table 8 presents the same information for the 2230 women in this age group who were discharged from the sanatorium for the first time during the same period. This includes the 559 who were

dead at discharge plus the 314 who have died since their first discharge. This gives a total of 873 (39.1%) of these women who are now dead in contrast to 21.8% of the 64 pregnant women who went to full term and were delivered at the sanatorium. Furthermore, 58 (6.6%) of the 873 died of non-tuberculous causes.

TABLE 8.—DATA ON ALL WOMEN 18-39 YEARS OF AGE WHO WERE DISCHARGED FROM THE SANATORIUM FOR THE FIRST TIME DURING 1924-1940, INCL.

Stage of disease.	No. disch.	Dead on discharge.		Interval in years between discharge and death.									Total deaths.		Non-tbc. deaths.	
		No.	%.	0-1.	1-2.	2-3.	3-4.	4-5.	5-10.	10 and over.	Un-known.	No.	%.	No.	%.	
Far adv.	1091	486	44.5	72	31	22	17	12	25	4	1	670	61.4	14	2.1	
Mod. adv.	637	50	7.8	32	14	9	8	9	19	6	..	147	23.1	13	8.8	
Minimal	242	6	2.5	2	2	1	1	12	5.0	2	16.7	
Extrapul.	93	13	14.0	2	2	1	5	23	24.7	10	43.5	
Undet.	167	4	2.4	7	1	..	1	2	3	3	..	21	12.6	19	90.5	
Total	2230	559	25.0	113	48	34	28	24	53	13	1	873	39.1	58	6.6	

Aside from the health of the consort, nothing affects the happiness and welfare of the family as much as children. Therefore, the 70 children born to these 64 mothers warrant some study. We were unable to trace 4 of this group, leaving 66 for further analysis. Of this group, 1 was still-born and 3 others have died of non-tuberculous conditions. Of the 62 who are living and whom we have been able to trace, 2 became tuberculin-positive while still in the preventorium, 1 of whom apparently acquired her infection from a grandmother who visited her frequently and who was later found to be tuberculous, but no contact has ever been established for the other one. The remaining 60 children are all well and as far as we know free from infection and disease.

TABLE 9.—PREGNANCY OCCURRING FOLLOWING DISCHARGE FROM SANATORIUM SUBSEQUENT TO THORACOPLASTIC OPERATIONS.

Single births only.	No. of mothers.			No. of babies.
	Now living.	Now dead.	Total.	
Single pregnancy	9†	1*	10	10
With 2 pregnancies	1	..	1	2
With 3 pregnancies	1	..	1	3
With 4 pregnancies	1*	..	1	4
Total	12	1	13	19

* Also included in full-term deliveries at sanatorium.

† Also included in premature group.

During the period 1921 to 1940, inclusive, 11 women whose pregnancy was recognized while they were patients in the sanatorium left the institution for various reasons to be delivered elsewhere. Of this group, we have no follow-up on 4. Of the remaining 7, 6 are alive and well, and 1 is dead. This girl returned to the sanatorium after delivery and died 22 months later. Of the 11 children who were born of these 11 mothers, all at the last report were living and well.

Up to January 1, 1941, we have followed 13 patients who had thoracoplasty operations at this sanatorium and who became pregnant following discharge. The number of pregnancies and the children born in this group are shown in Table 9. Two women in this group were included in the full-term group delivered at the sanatorium and 1 of the 2 was dead at the time of discharge. One other is included in the premature group but she had a full-term pregnancy later.

TABLE 10.—COMPARISON OF DEATH RATES OF PREGNANT WOMEN WITH ALL WOMEN 18 TO 39 YEARS OF AGE FIRST DISCHARGED FROM SANATORIUM (1921-1940, INCLUSIVE).

	Pregnant women.			All women.
	With full term delivery (incl. 2 who had had premature del.).	With premature delivery only.	Total pregnant women.	
Followed	86			
Not followed	4			
Total counted	82	6	88	2230
Deaths	15 (18.3%)	4 (66.7%)	19 (21.6%)	837 (39.1%)

One woman has been pregnant 4 times, another 3 times, another twice and the remaining 10 have gone through 1 pregnancy each.

These 13 women have given birth to 19 children all of whom were well at the last report.

Summary. Of 86 women, 18 to 39 years of age, whose pregnancy was allowed to go to full term during the years 1921 to 1940, 64 were delivered at the sanatorium and 22 were delivered elsewhere. Of the 82 followed up, 15 (18.3%) are dead in contrast to 39.1% of the women in the same age group who were discharged from the sanatorium for the first time during the same period. If those having premature deliveries are considered, 19 (21.6%) are dead in contrast to 39.1% of all women in the same age group who were discharged from the sanatorium for the first time during that interval.

While this group is too small to warrant definite conclusions, still the length of the study gives it some value. It seems to indicate that when the tuberculosis is properly treated pregnancy probably does not adversely affect the tuberculous process. This should be a great boon to those people who have wanted children but who have felt that they could not have them because of tuberculosis.

There are many variables which will require further study before we can explain why the death rate for all women 18 to 39 years of age following first discharge is approximately twice that of the pregnant group. It is, however, another factor influencing the conclusion that tuberculosis *per se* does not necessarily constitute an indication for therapeutic abortion. Conversely, if any condition should exist which would be considered an indication for therapeutic abortion if tuberculosis did not exist, then an abortion should be done even though tuberculosis does exist.

Treatment of the pregnant woman with tuberculosis by the most modern methods of combating the disease, together with equally modern prenatal care, apparently offers her as good a chance for recovery from her tuberculosis as though pregnancy did not exist. Perhaps a joint study by sanatoria holding the same views might yield figures large enough to be more nearly conclusive.

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SYSTEMIC REACTIONS TO MERCURIAL DIURETICS.

BY EDWARD M. KLINE, M.D.,

DEMONSTRATOR OF MEDICINE,

AND

W. B. SEYMOUR, M.D.,

INSTRUCTOR IN MEDICINE, WESTERN RESERVE UNIVERSITY SCHOOL OF MEDICINE,
CLEVELAND, OHIO.

(From the Department of Medicine of Western Reserve University School of Medicine and the Lakeside Hospital.)

DESPITE the general acceptance and widespread use of the organic mercurials as diuretics, little attention has been given the systemic reactions which sometimes occur. In papers dealing with the use of these drugs^{4,5,10,12,19,20} relatively little mention is made of their toxicity and many reports have appeared describing their use over long periods of time without mishap.^{3,7,8,13,14,16,17,23} However, aside from local toxic effects, certain generalized reactions have been reported.^{1,2,6,9,11,15,18,21,22,24} These are summarized in Table 1.

Five cases of systemic reactions to mercurial diuretics have come to our attention and, since these serve to illustrate some of the complications which are encountered, it seemed worth while to report them in detail.

Case Reports. CASE 1.—A 21-year-old white female, has been followed since 1933 in the out-patient department of this hospital. The diagnoses were: rheumatic heart disease with mitral stenosis and insufficiency, and auricular fibrillation. Decompensation finally necessitated the use of mercurial diuretics in January, 1937, and to March, 1941, she received a total of 22 injections, intravenous and intramuscular, of Salyrgan and Mereupurin without untoward effect. Since March she had had 10 doses of Mereupurin intravenously, 8 of which were followed by transient urticaria and the last 2 injections by a diffuse erythematous rash. At this point it was considered unwise to continue the use of the mercurial diuretics.

CASE 2.—A 44-year-old white male was admitted to this hospital for the first time on March 26, 1938, with a diagnosis of chronic myelogenous

leukemia. Ascites gradually developed and on June 4, 1940, he was given his first injection of 0.5 cc. of Mercupurin. Doses of 2 cc. were repeated on June 5, 8, and 9, 1940. There was nothing unusual about the patient's reaction to these injections and they were all followed by the customary diuresis.

TABLE 1.—DATA OF CASES OF SYSTEMIC REACTIONS TO MERCURIAL DIURETICS AS REPORTED BY OTHERS.

Author.	Sex.	Age (yrs.).	Injection following which reaction occurred.	Type of reaction.	Comment.
Parade ¹⁸	F	66	1	Angina and vomiting	
Hug ¹¹	Gastro-intestinal disturbances, 8; albuminuria and hematuria, 4; fever, 2; dermatitis, 1.	Reactions observed among 618 patients treated.
Derow ⁵	F	45	3	Albuminuria, hematuria, anuria, and azotemia.	Recovery.
Greenwald and Jacobson ⁹	M	2	3	Cyanosis, dyspnea, collapse and death.	Nephrosis.
	M	3	3	Convulsions, collapse, death.	Nephrosis.
Molnar ¹⁵	M	39	1	Cyanosis, dyspnea, death.	
Andrews ¹	F	22	1	Repeated convulsions.	Recovery.
Cadbury ²	F	63	2	Delirium and coma.	Recovery.
	F	47	6+	Collapse and convulsions.	
	F	21	3	Collapse and death.	
	M	5	1	Collapse and death	
Sundaram ²¹	M	10	1	Chest pain, collapse, death	
Wolf and Bongiorno ²⁴	..	4	5-6	Chills, fever, and rash after 5th injection; collapse and death after 6th injection.	
Tyson ²²	M	3	2	Convulsions, death within 1 min.	Nephrosis.
	M	27	5	Convulsion, cyanosis and cessation of respiration.	Nephrosis; final recovery.

On June 15, the patient received his fifth intravenous injection of Mercupurin. The dose of 2 cc. was unchanged but 2 hours following the injection he had a severe shaking chill and his temperature rose to 41° C. A similar reaction followed another injection of 2 cc. on June 24. No more mercurial diuretics were administered.

Death resulted on October 27, 1940, from intractable bleeding into the intestinal tract. Autopsy substantiated the clinical diagnosis of chronic myelogenous leukemia. There was no evidence of mercury nephrosis.

CASE 3.—A 49-year-old white male was seen for the first time May 4, 1939, in advanced cardiac failure resulting from long-standing hypertension. His first dose of Mercupurin of 0.5 cc. was given intravenously on May 7, 1939, and the second of 2 cc. on May 9. Both were followed by a good diuresis and no unusual symptoms. On May 13, a third dose of 2 cc. of Mercupurin was given intravenously. Three hours later the patient had a chill and the temperature rose to 39° C. Accompanying this rise in temperature there was marked dyspnea, cyanosis, nausea, and vomiting. Although the patient was greatly improved the following day there was a generalized morbilliform rash which persisted for about 72 hours. The temperature remained elevated and did not return to normal until the fourth day after the injection. No more mercurial diuretics were given at this time and he was discharged from the hospital greatly improved on May 26, 1939.

He was not seen again until August 1, 1939, at which time all of his symptoms had returned. There was tremendous anasarca and his weight had increased 40 pounds. Since 2 injections of Mercupurin had been given uneventfully, the reaction following the third injection was thought to be fortuitous. Accordingly, 2 cc. of Mercupurin were given intravenously (his fourth injection) and again the precise episode which had followed the third injection appeared. The chill, the dyspnea, the fever, and the rash all occurred in their proper sequence.

By September 18, the edema had accumulated to such a degree that he was completely incapacitated. Aminophyllin given intramuscularly in large doses was now without effect. It was decided to try a mercurial diuretic in the form of a rectal suppository (Mercurin). Following its use the patient experienced for the third time a severe reaction in every way identical with those that had occurred subsequently to the intravenous administrations of the drug.

He was hospitalized for long periods on two more occasions, but he continued in a state of chronic failure until his death on March 14, 1940. At autopsy the heart was dilated and weighed 500 gm. The coronary arteries were patent but they were the seat of marked arteriosclerosis with calcification. There was a healed infarct of the myocardium of the posterior portion of the left ventricle. Arteriosclerosis was generalized. There was no evidence of mercury nephrosis.

CASE 4.—A 57-year-old white male, whose illness had started abruptly in November, 1939, with myocardial infarction. His progress had been satisfactory until February, 1939, when he began to have edema and ascites. Salyrgan was administered (exact number of injections not known) intravenously and each time the patient complained of generalized pruritus following the injection; on two or three occasions he had also noticed a faint scaly erythema following its use. The patient was admitted to Lakeside Hospital September 26, 1939, where he was digitalized and given intermittent doses of ammonium chloride, Aminophyllin, chloral hydrate, and morphine sulphate. On October 2, 1939, 2 cc. of Salyrgan was given intravenously without any untoward effect. This was repeated on October 10, and was followed within 48 hours by severe generalized pruritus and an erythematous rash. The rash and pruritus persisted and on October 16 Salyrgan was given again. Immediately after this injection the patient complained of pain and burning in the tongue and throat, and the next day the generalized erythema was more intense. Pruritus was extreme. In spite of intensive local treatment the inflammation increased. The skin became thick, dry, and scaly, and over the thighs there were numerous deep excoriations which resulted from the patient's continuous scratching. Cardiac failure increased and the patient died on November 18, 1939.

At autopsy the heart was dilated and weighed 630 gm. There was a large healed infarct involving the anterior and apical portion of both ventricles. Microscopic examination of a typical area of skin showed a loss of stratified surface epithelium with marked perivascular infiltration of round cells and neutrophils. The capillary bodies of the corium were edematous. There was no evidence of mercury nephrosis.

CASE 5.—A 50-year-old colored male was seen for the first time in the Medical Out-patient Department of Lakeside Hospital on May 20, 1936. Over the past 4 months he had noted increasing dyspnea, and edema. The only essential feature of the past medical history was that he had had a hard chancre of the penis about 30 years before. The examination demonstrated an advanced aortic regurgitation and all the signs of cardiac failure. The Wassermann reaction was positive. The urine was normal, and the blood urea nitrogen was 13.5 mg. per 100 cc.

In spite of digitalization and some restriction of his activity, he did not improve and he was admitted to the hospital on July 6, 1936. He was given 1 injection of 2 cc. of Mercupurin intravenously with good diuretic effect and he was discharged after 20 days considerably improved.

Treatment of the patient's syphilis was begun on June 22, 1936. From this date until his final treatment on July 28, he received 6 intramuscular injections of bismuth at approximately weekly intervals.

He remained comfortable for about 6 weeks but after this period his dyspnea increased, and he was readmitted to the hospital on August 16, 1936. Fifteen hundred cubic centimeters of fluid were removed from the right pleural cavity and he was given 2 cc. of Salyrgan intravenously. Immediately his temperature rose to 39.3° C. and he became oliguric. The following chart shows his subsequent course:

Hospital day.	Intake.	Output.	Urine, sp. gr.	B.U.N.
1	2450	120		
2	1150	180	1.020	32.2
3	2660	130	1.015	37.6
4	1900	600	1.010	
5	1650	1280	1.010	67.5
6	1650	1930	1.010	

The patient became increasingly stuporous and irrational; on his sixth hospital day he died in convulsions. The urinary sediment during this period contained only occasional white blood cells, and the blood pressure continued essentially unchanged.

During his entire course the patient had received 4 intramuscular injections of bismuth. The last injection was given on July 26, 1936.

At autopsy there was cardiac hypertrophy and dilatation with syphilitic aortitis. The kidneys were of paramount interest. Grossly, they were enlarged, weighing 250 and 230 gm. The smooth capsule stripped easily, leaving a smooth yellowish-brown cortex. Tubular striations were apparent on the cut surface. Microscopic sections showed extensive degeneration of the tubules which were dilated. The lining epithelial cells were shrunken with granular eosinophilic cytoplasm and pyknotic nuclei. Hyaline casts and granular debris were seen in some lumina. Regenerating tubular epithelium was present in all sections. The glomeruli were normal, and the blood-vessels showed only slight sclerosis.

Discussion. This report illustrates that the systemic reactions to a mercurial diuretic vary considerably in their severity. Certain evanescent phenomena are to be anticipated occasionally with the use of any intravenous medication, and when these reactions occur as an isolated response they probably have no significance. Exceptions to this are instances where a sequence of injections produces identical reactions as in our first 2 cases. In Case 1 urticaria followed 8 consecutive injections, and in Case 2 a sharp rise in temperature followed immediately after 2 consecutive injections. Both patients had received previous identical injections without ill-effects.

Severe reactions are the shock-like responses which, if fatal, occur a few minutes after the injection or, if not, are delayed 2 or 3 hours. The symptoms of pulmonary edema exhibited by Case 3 are similar to those described in fatal cases, and it was these respiratory mani-

festations which lead Greenwald and Jacobson⁹ to consider them anaphylactic in nature. It is indeed perplexing to explain the identical reactions in this patient to both intravenous injections of Mercupurin and the Mercurin suppository. Comments in the literature deal with the systemic reactions to mercurials when given intravenously, and this is the only instance reported in which a severe reaction followed anything but intravenous or intraperitoneal¹⁵ administration.

An evanescent erythema followed the 2 final injections in Case 1, was part of the more severe general reaction in Case 3, and was seen as the only untoward manifestation to some of the early injections in Case 4. Later in this patient 2 intravenous injections of Salyrgan produced an inflammatory reaction of the skin which progressed to a typical exfoliative dermatitis. It is more than likely that these skin manifestations are warnings of more serious reactions to follow and should, we feel, contraindicate further use of the drug. An illustration is the case reported by Wolf²⁴ in which 4 injections had been given to a child without ill-effect. A fifth produced a transient morbilliform rash and a sixth injection, given a week later, was followed by sudden death.

The kidney has been studied more than any other organ for some deleterious effect of the prolonged use of the mercurial diuretics. Observations have consisted of analysis of urine over long periods of time followed by examination of the kidneys at necropsy. Due to numerous careful observations of this type it has been well agreed that the prolonged use of these preparations is practically never accompanied by significant renal damage.

Only 1 case of acute mercury poisoning⁶ is to be found in the literature, and although poisoning in this instance was severe the patient recovered. When death occurred sometime later from an unrelated cause the kidneys at autopsy showed no evidence of previous injury. The development of the acute nephrosis in Case 5 followed immediately after the intravenous injection of Salyrgan and there is little doubt that mercury was the immediate exciting agent. It is possible, however, that it was not the sole cause. The patient had received 6 injections of bismuth, and although the last dose was administered 19 days before the development of this syndrome, there may have existed a latent tubular damage which was greatly accelerated by the mercury. We must leave the matter unsettled. The condition may have resulted from mercury alone or from the two metals, bismuth and mercury.

Although it may at first appear that the reactions observed in these 5 patients are completely unrelated there is one important feature common to all. In each case the individual had received 1 or more intravenous injections without mishap. Later identical doses of the same drug produced systemic reactions of varying types and severity. It has been rather generally understood that

if a given individual tolerates the first intravenous injection of a mercurial diuretic he will have no trouble with subsequent ones. This is probably the reasoning behind the use of a small dose of the drug at the first injection. However, a review of these cases and the literature does not warrant this impression. In only 2 of the 7 fatal reactions reported (a total of 8 with our case) did death follow the first injection.

It is tempting to speculate on this point and to assume that injections, either intramuscular or intravenous, of an organic mercurial compound occasionally "sensitizes" the individual to subsequent injections. This explanation is, however, lacking true scientific confirmation. Nevertheless, it can be said with certainty that severe reactions to the mercurial diuretics are much more apt to follow any but the first injection. At the present time no prediction can be made as to when or under what circumstances a reaction is to be expected.

Summary and Conclusions. 1. Five cases exhibiting systemic reactions to mercurial diuretics are reported.

2. In 1 case the reaction to the use of a rectal suppository was identical to the reactions which followed 2 intravenous injections.

3. Reactions are more common after an individual has had several previous injections than after the initial injection.

4. Considering the wide usage of these drugs the frequency of reactions is very low.

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INEFFICIENCY OF IMMUNE GLOBULIN IN THE PROPHYLAXIS OF MEASLES DURING ADOLESCENCE.*

By J. ROSWELL GALLAGHER, M.D.,
SCHOOL PHYSICIAN, PHILLIPS ACADEMY, ANDOVER, MASS.

PRIOR to the reports of McKhann and Chu^{4a,b} in 1933 convalescent serum was considered to be the most satisfactory agent for the modification or prevention of measles,^{2,7} but the difficulty of obtaining sufficient quantities of convalescent serum has always restricted its use. Since the introduction of immune globulin (measles antibody) many reports of its use have appeared,¹ and it is generally agreed that this extract is of value in attenuating or preventing measles when given in proper doses and early enough in the incubation period. However, almost all the reports of its use have been concerned with prophylaxis in children of 10 years of age or less, and few reports deal with significant numbers of children of the adolescent period. Parish⁶ has described an outbreak of measles in a girls' boarding school in which about one-half of the 89 susceptible girls, ranging in age from 13 to 17 years, were given 4 cc. of immune globulin; 93% of the treated girls subsequently developed measles, and 75% of the untreated group became ill. Lyall and Murdick³ have reported two groups, one under institutional and the other under private care, ranging in age from 12 to 35 years, in which 33% and 43%, respectively, of treated individuals did not develop measles; however comparable figures for their 6 to 11 year age groups showed that 72% and 74% respectively of treated children did not develop measles. Other reports include only small numbers of individuals in the older age groups.

In a boys' boarding school the problem of attempting to control measles occasionally arises, and because of limited facilities for proper bed care, it may be desirable to attempt prevention rather than attenuation of the disease.

During the winter of 1941, following an extensive outbreak of influenza, a relatively severe type of measles developed in this school where there were 122 students who did not have a history of having had that disease. Many of these susceptibles had just recovered from influenza, the infirmary was crowded, and the students had lost much time from school; these seemed sufficient reasons for attempting to prevent measles, although in general it is believed that it is better practice to allow the individual to contract the disease in a modified form and to develop immunity.⁵ The dose of placental extract depends in part on the weight of the recipient, the effect desired, and the relation between time of exposure and time of inoculation.

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All individuals in this study ranged in age from 13 to 18 years and between 110 and 165 pounds in weight. Prevention rather than modification was the object of the treatment; and all susceptibles were inoculated as soon as possible without waiting for a history of definite exposure. Eighty-four students were given 8 cc. of immune globulin intramuscularly; the remaining 38 susceptible students were given no treatment chiefly because they did not appear when first summoned, or, in a few instances, because parental objection was anticipated, but no other factors operated in the selection of this control group.

Results. It will be seen in Table 1, that 52% of the group of 38 susceptibles who were not given measles antibody developed measles within the 28-day period of observation. Cases developing after 28 days have not been included because it is believed that the protection period of immune globulin is short.⁵ During that 28-day period, 34 individuals (40% of the inoculated group) developed measles; however, 6 of these students developed measles within 4 days of the time of their inoculation, and it is unlikely that an attempt at prophylaxis so late in the incubation period would be effective, and if these 6 cases are excluded, it can be said that 33% of the inoculated group developed measles more than 4 days and less than 28 days after treatment. If one believes that students of this age and weight should receive a dose of this size early in the incubation period if it is to be effective, it is reasonable to exclude the 15 individuals who developed the rash of measles less than 10 days after the time of inoculation; of the remaining 69 students, 19 (27%), developed measles more than 10 days and less than 28 days after that treatment. Because of the brevity of the protection period it is of interest to note that only one of these 19 individuals developed measles more than 16 days after his inoculation. Five of these 19 students had a relatively mild type of measles which apparently had been modified; only one of the non-inoculated group had a measles of similar mildness. None of the cases in either group developed any complications.

TABLE 1.—RESULTS OF PROPHYLACTIC USE OF IMMUNE GLOBULIN.

	Inoculated.	Not inoculated.
Number of students	84	38
Age range	13-18 years	13-18 years
Weight range	110-165 lbs.	115-160 lbs.
Developed measles within 28 days of inoculation	34 (40%)	20 (52%)
Developed measles between 5th and 28th day after inoculation	28 (33%)	
Developed measles between the 11th and 28th day after inoculation	19 (22%)	
Developed modified or mild measles	5	1

From these data it seems probable that the immune globulin in that dosage had some immunizing effect, but it is evident that this effect was far from reliable and somewhat questionable. It is

significant that 14 individuals who had been given 8 cc. of immune globulin more than 10 days and less than 17 days before the development of their rash showed no modification of the disease. The evaluation of immune globulin for the prevention of measles in this age group obviously requires further investigation: the size of dose and potency of the extract used are two variables which might well affect the results obtained.

Thirty of the 84 students inoculated had a relatively severe reaction with pain at the site of injection, fever of short duration, and malaise. Eight of the 19 students who developed measles between the 10th and 28th day after inoculation had severe reactions; of these 8, 3 had modified measles.

Summary. 1. Eighty-four males ranging from 13 to 18 years of age were given 8 cc. of immune globulin (measles antibody) in an attempt to prevent measles. Thirty-eight males of similar age range were given no prophylaxis.

2. Forty per cent of the treated group developed measles within 28 days, and 52% of the untreated group developed measles within the same period. Of the 69 students inoculated more than 10 days before the rash appeared, 19 (27%) developed measles, and 5 of these cases were modified.

3. It is suggested that a dose of 8 cc. of immune globulin given early in the incubation period is not an efficient agent for the prevention or modification of measles in this age group; but the variation of success with differences in potency of extract and size of dose is emphasized.

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THE EFFECT OF DRUGS ON THE CIRCULATION IN NORMAL HANDS AND FEET.

BY HUGH MONTGOMERY, M.D.,

ASSOCIATE IN MEDICINE, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA, PA.

(From the Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania, and the Department of Pharmacology, University of Pennsylvania.)

THE classification of drugs into "vasodilators" and "vasoconstrictors" suggests a simplicity which may mislead those attempting to secure their effects therapeutically. It is impossible to conceive of a considerable generalized dilatation of all vessels in the body without assuming an increase in total blood volume, a type of

physiologic response which is believed to take place only slowly. Therefore, when large doses of the rapidly acting vasodilators are given to normal subjects and some vessels, as in the face, regularly dilate, other vessels must constrict. Obviously, therefore, clinicians cannot assume if the patient is given a drug classified as a "vasodilator" that the vessels of the extremities will dilate.

The purpose of this paper is to present studies of the effects of various drugs upon the circulation of blood through the hands and feet, to compare these effects with those of physical agents and the effect of vasomotor paralysis, and to help clear the way for further investigation of methods, pharmacologic and otherwise, to increase peripheral bloodflow in patients with insufficient peripheral circulation.

The conclusions are based on measurements of bloodflow, pulse rate, and blood pressure, made in this clinic on normal subjects. Measurements of other investigators and recognized therapeutic effects are referred to briefly and are drawn upon freely to help produce Figure 1.

Methods. The subjects were 26 young adults free of disease and 4 patients, aged 21, 31, 41 and 50, who had no cardiovascular disease or fever; only 7 were women.

Digital bloodflow was measured by one of two methods: by plethysmograph* or by skin temperature or by both. Rapid fluctuations in bloodflow were measured only by the plethysmographic method, because the skin temperature method has a several minute lag. Bloodflow in the toes was measured only by the skin temperature method, because it is difficult to fit a plethysmograph to a toe. All figures for bloodflow, including skin temperature figures, are reported as cc. of blood per 100 cc. of tissue per minute. Skin temperature figures were converted to cc. of blood per 100 cc. of tissue per minute by means of a graph previously published.¹³ By reporting cc./100 cc./minute instead of skin temperature *changes* in values become more significant. For instance, using a room temperature of 20° C. a skin temperature difference of 4° C. between 26° and 22° C. indicates a bloodflow change of only 6 cc./100 cc./minute, whereas a skin temperature difference of 4° C. between 34° and 30° C. indicates a bloodflow change of about 60 cc./100 cc./minute.¹³

Blood pressure was taken from the upper arm by the usual Riva Rocci method. Pulse rate was counted directly or taken from the pulse waves photographed during plethysmography. Room temperature was kept constant, and in only a few cases was a thermostatically controlled room required and used. It is regretted that body temperature was recorded in only 27 of the 56 experiments. Body temperature was taken by a clinical thermometer kept for 5 or more minutes in the mouth. Cardiac output was measured only twice, in the case of induction of maximal vasodilatation by reflex heat, and during vasodilatation from alcohol. No considerable change in cardiac output resulted.†

When drugs with brief action were studied, more than one drug was administered on a single day; but in no instance is a measurement reported when there was reason to suspect overlapping of drug effects. In the case

* Dr. Burton made the plethysmographic measurements by a method recently described by him.⁵

† Dr. Isaac Starr made the measurements of cardiac output during peripheral vasoconstriction and subsequent vasodilatation.

of drugs with rapid effects on bloodflow only the plethysmographic method of measurement was used, because of the time lag, previously mentioned, of skin temperature. Vasodilator drugs were used only when vasodilatation was incomplete. With the exception of the use of alcohol (whisky by mouth) the identity of the drug was unknown to the subject until the experiment was completed. The subjects refrained from food 2 or more hours prior to each investigation. Each subject reclined lightly clothed. The various measurements were made until they became constant.

In preparation for the use of drugs by hypodermic administration the effect on bloodflow in 10 subjects of 0.1 to 0.4 cc. of sterile water was measured. A slight increase or no increase in pulse rate, little if any change in blood pressure, and a transient decrease in bloodflow usually resulted. In some instances the anticipation of needle-prick caused a similar transient change, quite distinguishable from the effects of drugs.

Results. *Amyl nitrite* was administered 15 times in all, to 11 subjects. The subject inhaled the drug for $\frac{1}{2}$ to 1 minute. Before administering the drug pulse rate, blood pressure, and bloodflow averaged 76/minute, 118/76 mm. Hg, and 30 cc./100 cc. tissue/min-

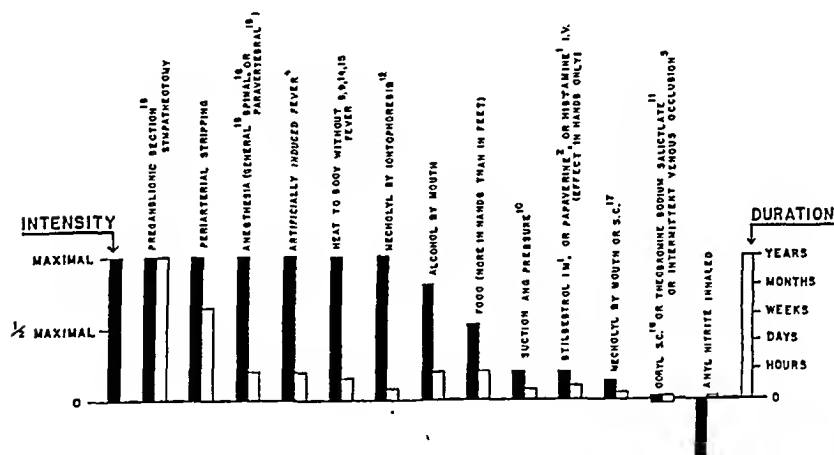


FIG. 1.—Approximate relative effectiveness of various drugs and procedures in increasing bloodflow in the hands and feet of normal subjects. "s.c." = subcutaneously; "i.v." = intravenously. The numbers given with the procedures refer to the bibliography concerning the individual procedures.

ute respectively. After taking the drug the pulse, blood pressure, and bloodflow in the fingers reached maximum change values (average) of 109, 98/58, and 5 in the average time of 1.4 minutes. In all instances pulse rate increased markedly (average +33), blood pressure fell sharply (av. -20/-18) and bloodflow in the fingers decreased (av. -25) in response to the decrease in blood pressure. On the average, all effects of the drug had ceased within 4 minutes after beginning, 3 minutes after ending, inhalation. Bloodflow was not measured in the toes because the plethysmographic method is not readily adapted to use on the toes and measurements of skin temperature are not sensitive to the rapid rate of changes under

amyl nitrite. The expected flushing of the face and feeling of "fullness" in the head occurred in all subjects. In other subjects, not listed here, bloodflow increased consistently in the skin of the face (skin temperature) and in the oral mucosa (thermostromuhr).

Mecholyl (acetyl-beta-methylcholine chloride) was injected *subcutaneously* 6 times in all in 5 subjects. Doses were varied from 4 to 1 mg. in an unsuccessful attempt to cause a significant increase in peripheral bloodflow. Pulse rate usually increased (av. +23) and blood pressure usually fell (av. -7/-10). Bloodflow changes were variable and were neither striking nor sustained (av. +8 in finger, -2.5 in toe). Judging from the blood pressure and pulse the effects of the drug became maximal in 4 (average) minutes after injection and ceased after 16 (average) minutes. A single dose of 12 mg. increased the pulse rate by 55 beats, lowered the blood pressure by 15/20 and decreased the finger bloodflow by 27 cc./100 cc./minute.

Mecholyl by mouth (acetyl-beta-methylcholine bromide) was given to 5 subjects in doses of 0.4 to 0.8 gm. No significant change in pulse rate (av. +3), blood pressure (av. -3/-2) or bloodflow in the toes (av. 0) resulted. An increase in finger bloodflow of 6 may possibly be significant. No significant difference resulted from the different doses used. Mouth temperature tended to fall slightly (av. -0.2° F.), at average room temperature, 21° C.

Doryl (beta-methyl-choline urethane) was injected subcutaneously into 7 subjects. Doses were varied from 0.5 to 0.1 mg. in an unsuccessful attempt to cause a significant increase in peripheral bloodflow. Pulse rate changed insignificantly (av. +2, largest dose +10). Blood pressure either remained constant or fell slightly (av. -7/-4), largest dose -25/-15). Bloodflow was not significantly altered (av. -3, finger; -5, toe). Since the average effects on pulse rate, blood pressure, or bloodflow were insignificant, no conclusion can be drawn concerning the time of maximal effect or the duration of effect of the drug. No significant differences resulted from the different doses used.

Papaverine hydrochloride was given intravenously to 6 subjects in doses of .015 to .05 gm. ($\frac{1}{4}$ to $\frac{3}{4}$ gr.). There was no significant change in pulse rate (av. +1), blood pressure (av. 1/1) or bloodflow in the toes (av. 0). The bloodflow in the fingers increased markedly in 4 of the 6 instances, remained constant in 2 (av. +31). The maximum increases in finger bloodflow occurred in from 25 to 38 minutes (av. 30) and some effect lasted for a little more than 1 hour. Mouth temperature tended to fall but rose a degree in 1 instance (av. -0.1° F.). Room temperature averaged 22° C.

Food was given to 8 subjects who had received no food for more than 3 hours. It consisted of a palatable light or very light lunch with little or no hot food or drink. In every instance the pulse rate increased slightly (av. +10) and the blood pressure rose slightly

TABLE 1.—EFFECTS OF VASODILATOR DRUGS AND PROCEDURES ON PULSE, BLOOD PRESSURE AND BLOODFLOW IN THE HANDS AND FEET.

Date.	Subject and sex.	Age.	Wt.	Room temp. °C.	Dose.	Pulse rate.			Blood pressure.			Bloodflow.				Changes induced.									
						Before drug.	Max. eff.	Time of max. eff. (min.).	Dur. of any eff. (min.).	Before drug.	Max. eff.	Time of max. eff. (min.).	Dur. of any eff. (min.).	Before drug, cc./100/min.	Max. effect, cc./100/min.		Time of max. eff. (min.).	Dur. of any eff. (min.).	Pulse rate.	B.P.	Bloodflow.				
															Fin.	Toc.					Fin.	Toc.			
5-16-38	M. A. (M)	22	172	26	...	88	102	0.5	2	120/70	110/70	0.5	2.5	40	..	5	..	1	1.5	+14	-10/-0	-35	-10/-0		
5-17-38	A. R. (F)	23	112	26	...	80	115	1.5	5	120/75	110/65	1.5	5	50	..	5	..	1	..	+35	-10/-10	-45	-10/-10		
5-18-38	L. S. (M)	23	170	25	...	83	108	2	4	100/75	100/60	0.5	2	15	1	..	1	..	3	4	+25	0/-15	-14	0/-15	
5-23-38	J. W. (M)	23	156	25	...	80	100	1.5	2	113/75	105/60	1.5	2.5	45	..	1	..	2	2	+20	-8/-15	-44	-8/-15		
5-21-38	I. S. (M)	23	170	27	...	70	85	2	3	105/70	70/50	2	3	3	..	1	..	1	1	+20	-40/-30	-2	-40/-30		
5-16-39	G. M. (M)	23	...	20	...	70	85	3.5	4.5	100/75	95/65	2.3	3	20	10	..	1	2	2	2	+15	-35/-20	-10	-35/-20	
5-17-39	R. S. (M)	23	165	21	...	70	115	1	1.5	125/90	105/30	1	5	2	..	0.5	1	+40	-20/-15	-38	-20/-15		
5-18-39	J. E. (M)	24	175	25	...	105	130	1	2	120/70	110/50	2	2.5	4	..	2	..	2	..	+35	-20/-60	-2	-20/-60		
5-22-39	W. H. (M)	25	153	29	...	75	120	2	2.5	115/75	90/70	1.5	2	15	..	13	..	0.5	1	+25	-15/-20	-87	-15/-20		
5-23-39	R. W. (M)	23	140	27	...	60	110	1	1.5	120/80	90/60	1	5	4	..	7	..	2	7	+45	-25/-5	-3	-25/-5		
5-21-39	S. R. (M)	22	175	26	...	55	110	1	5	140/60	80/40	1	4	35	2	2	..	1	2	+50	-60/-20	-33	-60/-20		
Averages	25	...	76	109	1.5	4.0	118/76	98/58	1.4	3.1	30	..	4.6	..	1.4	3.2	+33	-20/-18	-25	-20/-18		
5-17-38	A. R. (F)	23	112	26	4 mg.	75	120	0.5	20	100/65	80/50	2.5	5	18	..	1	..	10	35	+45	-20/-15	-17	-20/-15		
5-19-38	J. K. (F)	26	136	27	4 mg.	87	107	3	8	100/75	100/75	2	..	2	+20	0	0	0		
5-25-39	R. J. (M)	25	158	26	1 mg.	50	60	4	6	110/65	110/65	+10	0	0	0		
3-11-41	F. B. (M)	21	120	23	2 mg.	55	70	5	6	110/75	110/55	5	18	40	..	30	..	+15	0/-20	+32	0/-20		
3-11-41	A. S. (F)	28	120	23	1 mg.	68	88	3	9	122/72	100/50	7	40+	39	2	65	2	34	34+	+20	-22/-22	+26	-22/-22		
Averages	25	...	84	114	4	16	90/50	90/50	8	3	3	42+	42+	+30	0		
5-16-38	M. A. (M)	22	172	26	12 mg.	70	93.1	3.3	11	105/67	98/57	4.8	21+	20	5	27	2.5	29+	37+	+23	-7/-10	+8	-7/-10		
2-21-41	M. N. (M)	31	125	22	0.4 gm.	76	76	118/75	103/55	4	9	30	..	3	..	2	15	+55	-15/-20	-27	-15/-20		
2-21-41	O. K. (F)	22	100	21	0.4 gm.	96	96	108/70	108/70	17	2	3	2	50	60+	0	0	-14	0		
2-25-41	H. M. (M)	36	140	21	0.6 gm.	70	82	10	20	109/72	109/68	..	15	4	2	4	2	+12	-2/-5	+11	0	0	
2-27-41	E. T. (M)	11	157	20	0.8 gm.	71	76	122/80	111/60	38	83+	70	2	105	2	53	40+	+2	-11/0	+35	0	-4	
3-10-41	E. T. (M)	11	157	20	0.4 gm.	60	60	134/80	130/76	7	42+	10	6	10	3	40+	40+	0	-4/-1	0	-3	-2	
Averages	21	...	75	78	119/75	115/73	18	46+	21	2.8	27	2.2	60+	70+	+3	-3/-2	+6	-3/-2		

DORYL (STURCTANVENOUSLY).									
5-10-38	J. K. (F)	26	136	27	0.25 mg.	100	100	100	100
5-25-38	J. L. (M)	21	155	27	0.25 mg.	80	85	100	100
5-20-38	R. G. (M)	34	162	25	0.50 mg.	70	80	80	85
2-25-41	H. P. (M)	38	140	21	0.20 mg.	60	60	60	60
2-25-41	P. T. (M)	32	160	22	0.20 mg.	68	58	60	60
3-10-41	E. T. (M)	41	157	20	0.10 mg.	60	60	60	60
3-11-41	F. B. (M)	21	120	23	0.10 mg.	68	72	72	72
Averages	23	...	72	74	74	74
1-28-41	G. D. (M)	50	200	21	4 oz.	76	76	76	76
1-30-41	J. G. (M)	24	165	21	4 oz.	64	76	76	76
1-31-41	A. S. (F)	28	120	21	2 oz.*	68	80	80	80
2-4-41	H. M. (M)	36	180	22	1 oz.†	72	76	76	76
2-20-41	W. D. (M)	26	197	21	4 oz.†	64	74	74	74
Averages	21	3 oz.	66	66	66	66
2-21-41	M. N. (M)	34	125	22	0.25 gr.	71	71	71	71
2-20-41	W. D. (M)	26	197	21	0.5 gr.	60	60	60	60
2-20-41	H. M. (M)	36	180	23	0.5 gr.	52	56	56	56
2-25-41	H. P. (M)	38	140	21	0.75 gr.	60	60	60	60
3-10-41	E. T. (M)	41	157	20	0.50	84	76	76	76
3-11-41	A. S. (F)	28	120	23	0.25	67	68	68	68
Averages	22	...	74	74	74	74
1-31-41	A. S. (F)	28	120	23	Light	68	72	72	72
2-21-41	M. N. (M)	31	125	22	Light	56	64	64	64
2-27-41	J. M. (M)	40	184	21	Med.	68	68	68	68
2-27-41	H. M. (M)	36	180	21	Light	61	76	76	76
2-28-41	L. K. (M)	31	335	20	Light	102	114	114	114
2-28-41	P. T. (F)	31	107	21	Light	74	86	86	86
3-10-41	E. T. (M)	41	157	20	Light	72	82	82	82
3-11-41	A. S. (F)	28	120	23	Med.	72	82	82	82
Averages	21	...	72	82	82	82

* Whisky taken 70 minutes after the preceding.

+ Whisky taken 40 minutes after the preceding.

† Whisky taken 48 minutes after the preceding.

(av. +12/6). Pulse rate, blood pressure, and finger bloodflow were maximal in an average of 26, 9, and about 60 minutes respectively, and lasted for more than $1\frac{1}{2}$ hours. In all but 1 instance the finger bloodflow increased (av. +31) but no really significant change in bloodflow in the toe resulted (av. +5).

Alcohol (whisky diluted by tap water) was taken orally 8 times in all by 5 subjects in doses of 1 to 4 ounces. Pulse rate was not significantly changed (av. +4). Blood pressure was slightly raised (av. +9/+10) with this maximum effect at an average of +13 minutes and with some elevation persisting for an average of 34 minutes. Only in 1 instance were measurements of finger bloodflow made, then 1 ounce of whisky was taken and the bloodflow increased by 62 cc./100 cc./minute and in that instance no increase in bloodflow in the toe resulted. In all 8 doses of alcohol the bloodflow in the toes increased (av. +22). In all but 1 instance mouth temperature fell (av. $-.3^{\circ}$ F.) at average room temperature 21° C. Striking increases in bloodflow in the toes resulted in all of 4 subjects by pushing the dose of whisky to 4 or 6 ounces (av. rise of 42 cc./100 cc./minute). This is approximately a maximal rate of bloodflow for the toes.

Heat was applied to the body in 2 instances. The results verify the strong impression that vasodilatation occurs more readily in the hands than in the feet.^{1,2,8,15} In the first subject with a 0.2° F. rise in mouth temperature the finger bloodflow rose from a level of 20 to a level of 115. The bloodflow in the toe failed to rise until further body heat accumulated. With the further rise of 0.2° F. in mouth temperature the bloodflow in the toe rose from a level of 2 to a level of 50. The same experiment with another subject gave similar values: with a 0.3° F. rise in mouth temperature there was a rise of finger bloodflow from 2 to 110, with a constant flow in the toe of 2; and with a further rise in mouth temperature of 0.2° F., there was an increase in bloodflow in the toe from 2 to 40.

Discussion. Measurements of bloodflow in the human extremities have previously been reported with insufficient emphasis upon factors which are important if the measurements are to be compared with those of other investigators. Attention to these factors helps to clarify some differences of opinion of the usefulness of various agents and drugs advocated for increasing bloodflow. A falling body temperature decreases peripheral bloodflow, a rising body temperature increases it.¹⁰ Environmental temperature changes will influence body temperature and alter peripheral bloodflow accordingly.^{14,15} Pulse rate reflects blood pressure and cardiac output changes to some extent, through carotid sinus and cardiac accelerator and depressor mechanisms, and indicates changes in the circulation centrally as well as peripherally. Blood pressure when decreased may call in cardiac accelerator and peripheral vessel constrictor changes, and when increased may slow the heart and even

reduce cardiac output. Great variations in effect result from different doses and routes of administration of some drugs.

In general, then, measurements of peripheral bloodflow changes, made to evaluate the usefulness of agents intended to promote bloodflow, should be accompanied by the following measurements: 1, bloodflow in the foot as well as in the hand; 2, mouth or rectal temperature, 3, environmental temperature; 4, pulse rate, 5, blood pressure; and 6, listing of doses and routes of administration of drugs.

Skin temperature measurement is a reliable method of measuring digital bloodflow with the exception that there is a time lag of several minutes' duration, and for this reason rapid changes in flow are not accurately recorded. The simplicity of the skin temperature method, however, makes it ideal for the study of sustained changes in digital bloodflow induced by therapeutic agents. Bloodflow data should be presented as cc. blood/100 cc. tissue/minute, or as temperature °C., but should not be presented *solely* as a *difference* in flow or a *difference* in skin temperature.

Agents to be avoided as variables in any study of peripheral bloodflow are: 1, food; 2, heat or cold externally or internally; and 3, smoking. The reaction of peripheral bloodflow to pain or to startle is a variable and is conspicuous; but it is brief if the stimulus is momentary and it is readily distinguished from more useful, sustained effects.

A study of the influence of several promising drugs and other factors upon digital bloodflow in normal subjects shows that digital bloodflow is augmented by these agents in the following order of intensity: 1, heat to the body sufficient to raise the body temperature slightly; 2, alcohol by mouth, such as whisky in doses of 2 to 6 ounces; 3, food; 4, papaverine intravenously; and 5, mecholyl by mouth. The approximated optimum doses and routes of dosage of the drugs are given.

Certain powerful vasodilator drugs *decrease* peripheral bloodflow, probably because they have selective vasodilator action elsewhere or because they induce peripheral vasoconstriction by the carotid sinus reflex: amyl nitrite by inhalation, mecholyl (12 mg.), and doryl by hypodermic (0.5 mg.). In these instances the blood pressure falls.

The list of drugs affecting the peripheral circulation is, of course, incomplete. However, from this list and from studies elsewhere, especially from the recent work of Abramson, Zazeela and Schkloven,¹ it is possible to present the relative effectiveness of a greater variety of drugs and procedures that increase peripheral bloodflow. (See Fig. 1.) This order of effectiveness is approximate, is based on maximum effective and safe dosage, and fails to hold when the variables listed under "Discussion" are not controlled. When vasodilatation has almost been induced by some set of circumstances, a drug of low vasodilator potency may be entirely effective, whereas

a drug high in the list may be ineffective when the subject has severe peripheral vasoconstriction at the time of its administration.

The effect on bloodflow of exercise, of suction and pressure therapy, and of intermittent venous occlusion should be mentioned. Though exercise is known to increase bloodflow conspicuously in muscle, it probably has little effect upon bloodflow in digits. Alternate suction and pressure therapy is designed to force blood through fixed channels rather than to cause vasodilatation.¹⁰ The beneficial effect of intermittent venous occlusion rests on an unknown basis and with its use no consistent increase in peripheral bloodflow has been found.³

Summary. Measurements of digital bloodflow were made in normal subjects given vasodilator drugs. Consideration was given to the normal factors influencing bloodflow, *i. e.*, food, environmental temperature and exercise. The approximate effectiveness of various normal and operative procedures and drugs intended to increase peripheral bloodflow are indicated in Figure 1.

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BOOK REVIEWS AND NOTICES

CONCEPTUAL THINKING IN SCHIZOPHRENIA. By EUGENIA HANFMANN, PH.D., Instructor of Psychology, Mount Holyoke College, and JACOB KASANIN, M.D., Chief Psychiatric Service, Mount Zion Hospital, San Francisco, Assistant Clinical Professor of Psychiatry, University of California Medical School. Pp. 115; 1 colored plate. New York: Nervous and Mental Disease Monographs, No. 67, 1942. Price, \$2.50.

KRAEPELIN regarded the disordered thinking of the schizophrenic as a "disturbance of association." Since the day of that Master, various theories have been advanced. Recently, the Russian psychologist, Vigotsky, thought that the basic disorder was a conceptual impairment, leading to regression in thinking complexes, similar to those of children up to 14 years; both classes show incapacity for the abstract thinking of the more mature, normal person. In this study, the effort has been to verify or modify the conclusions of Vigotsky. The Concept Formation Test, originated by Ach and modified by others, was the method Vigotsky employed. It consists in the use of 22 blocks varying in size, shape, height and color. On the bottom of each block is one of four nonsense words: *lag, bik, mur, cev*. After much detailed instruction, aided by the use of a colored illustration, the blocks are shuffled and the subject is put to the test. Briefly, it is to be noted what characteristic of the blocks the subject employs, in bringing about a grouping that shall cause all the blocks carrying the same nonsense word, to appear in one group. It is claimed the plan offers the opportunity for the formation of both complexes and conceptual thinking. Tests were made with 62 schizophrenics, 24 subjects with organic disease (paresis and arteriosclerosis), and 95 normal controls. Others have assumed there are different levels of thinking, which by these authors are arbitrarily named primitive, intermediate, and highest or conceptual levels. Working with these levels, it is their belief that most schizophrenics show impaired conceptual thinking; however, they maintain that not all normal persons respond satisfactorily at the conceptual level, nor do all schizophrenics fail to do so. N. Y.

ENCEPHALITIS, A CLINICAL STUDY. By JOSEPHINE B. NEAL, L. BENDER, H. HARRINGTON, R. S. MUCKENFUSS, T. J. PUTNAM, A. A. ROSNER and L. D. STEVENSON. Pp. 563. New York: Grune & Stratton, 1942.

THIS book appears in good time, because epidemiologic curves strongly suggest that, war or no war, the outbreak of another influenza epidemic can be expected in one of the next few years. Influenza epidemics, on the other hand, have been often accompanied or followed by epidemics of encephalitis, although the intrinsic relationship between the two diseases is far from clear. A few of the many problems connected with this question have been solved during the 25 years following the last pandemic. It seems to be an established fact today that the clinical entity "influenza" is caused by one of two specific viruses and that Pfeiffer's influenza bacillus plays only the rôle of an occasional secondary infectant. However, the influenza virus does not seem to be the causative agent of encephalitis of the lethargic type. In fact, just this type of encephalitis—in contrast to

the St. Louis, the Japanese and the equine form—has not yet yielded a virus transferable to animals or cultivable in embryonic tissue. Yet, more men have probably suffered from lethargic encephalitis and its sequelæ than from all other forms together.

This book is arranged around the clinical course, the medical treatment of the acute stage of this disease and its late sequelæ (Neal), the surgical treatment of tremor, rigidity and blepharospasm (Putnam), psychiatric sequelæ (Rosner) and the behavior disturbances of children following encephalitis (Bender). Dr. Neal reports her extensive clinical experience gained from the observation of 800 cases of encephalitis, some of them checked over a period of 5 and more years. Well-selected histories ably illustrate the various phases and complications of this disease. A chapter on the neurologic complications of acute infections and vaccinations (Neal) supplements the clinical part of the book. However, it is an understatement to call this publication a "clinical study." One-fourth of the monograph is dedicated to the pathology of encephalitis and encephalopathy. Stevenson describes with rare completeness the manifold varieties in this field based mainly on personal experience. A number of well-reproduced photomicrographs illustrates the text. It is certainly stimulating to hear different authors discuss the same topic from various viewpoints. Many chapters of the book are accompanied by an exhaustive bibliography. This monograph may easily become the standard clinical and pathologic guide-book for the coming encephalitis epidemic.

F. L.

FOUR TREATISES OF THEOPHRASTUS VON HOHENHEIM CALLED PARACELSUS.

By C. LILIAN TEMKIN, GREGORY ZILBOORG, GEORGE ROSEN, HENRY E. SIGERIST. Edited, with a Preface by HENRY E. SIGERIST. Translated from the original German, with Introductory Essays. Pp. 256; 1 illustration. Baltimore: The Johns Hopkins Press, 1941. Price, \$3.00.

THIS English translation of four important treatises by Paracelsus, the great Swiss rebel against the medical traditionalism of the medical faculties of his day, is presented in commemoration of the 400th anniversary of his birth on September 24, 1541. As Dr. Sigerist explains in the Preface, they were chosen to illustrate four different aspects of his work. The first, the *Sieben Defensiones*, reveals the man and his fundamental ideas; the second, *Von der Bergsucht*, one of the earliest works on an occupational disease, opened a new line of medical writing; the third, *Von der Krankheiten*, is "the most important document on [his] psychology and psychiatry;" and the fourth, *Liber de nymphis, sylphis*, . . . (written in German, in spite of its Latin title) was included by Dr. Sigerist as a sample both of contemporary art and literature and of Paracelsus' philosophy and theology. We are again indebted to the Hopkins Institute for this scholarly contribution toward "reviving the personality of an honest man who was a great physician and a staunch fighter for what he considered the truth." It is made the more entertaining and instructive by the Preface and the introductory essays to each translation.

E. K.

THE TREATMENT OF BURNS. By HENRY N. HARKINS, M.S., M.D., Ph.D., F.A.C.S., Associate Surgeon, Henry Ford Hospital, Detroit; Formerly Instructor in Surgery, University of Chicago; John Simon Guggenheim Memorial Fellow in Surgery, 1938-1939. Pp. 457; 120 figures, 40 tables and 16 charts. Springfield, Ill.: Charles C Thomas, 1942. Price, \$6.50.

SINCE in these busy days most medical books are used as reference books and are not read from cover to cover, the author has done himself an injustice in the title he has chosen for this book. This is a monograph on the

history of the development of our knowledge of the effect of burns on the body and of the general and local treatment of burns. The bibliography contains over 1300 references to the literature.

This is a book to be recommended to a student of the subject of burns as well as to the clinician, though the clinician will find most of his information in Part IV. It is the most complete volume on the subject which is available. I. R.

ACUTE ALCOHOLIC INTOXICATION, A Critical Review. By HENRY W. NEWMAN, M.D., Assistant Professor of Medicine (Neuropsychiatry) Stanford University School of Medicine. Pp. 207. Stanford University: Stanford University Press, 1941. Price, \$2.50.

YEARS ago, if a man got drunk, he might at most beat his wife and children. Now, as the driver of a motor car, he can bring death and destruction to the public. The increasing medico-legal importance of the subject has stimulated research, the results of which are critically reviewed in this volume by one who is himself an active investigator in the field. Part I deals with the general action of ethyl-alcohol, including chapters on absorption and distribution, on excretion and on combustion. Part II, on the toxicology of ethyl alcohol, has chapters on acute toxicity, on the chemical diagnosis of drunkenness (the data here are particularly well presented), and on the treatment of acute alcohol intoxication. To each chapter is appended an adequate bibliography. There are many gaps in our knowledge of the subject and many of its aspects are still controversial. The author is therefore all the more to be commended upon the excellence of his presentation and evaluation of the material. The book is interesting, useful and stimulating. R. K.

FOOD AND BEVERAGE ANALYSES. By MILTON A. BRIDGES, B.S., M.D., F.A.C.P., Late Director of Medicine, Department of Correction Hospitals, New York; Consulting Physician, Seaview Hospital, Staten Island, New York, etc., and MARJORIE R. MATTICE, A.B., M.S., Assistant Professor of Pathological Chemistry, Department of Medicine, New York Postgraduate Medical School, Columbia University; Chief Chemist, New York Postgraduate Hospital. Pp. 344. Second Edition. Philadelphia: Lea & Febiger, 1942. Price, \$4.00.

A COMPILATION of analyses of a wide range of natural foods, cooked foods, packaged foods and beverages, including many common brands. The material is set forth in well-arranged tables. This second edition, somewhat larger than the first, includes much new material, notably data on the acidity of foods, their fiber content, the occurrence of sulphur, bromine, calcium, oxalate, phytins, purins, available carbohydrates, and ionizable iron. Miss Mattice, who assisted the late Dr. Bridges in the preparation of the first edition, is to be complimented on the excellence of the present volume. It will be welcomed by all who deal with the practical problems of nutrition. R. K.

LIFE AND DEATH AT LOW TEMPERATURES. By B. L. LUYET, Professor of Biology, and P. M. GEHENIO, Instructor in Biology, St. Louis University. (No. 1 of a series of monographs on general physiology edited by B. J. LUYET.) Pp. 341; 33 illustrations. Normandy, Mo.: Biodynamica, 1940. Price, \$4.50.

ONE of the most important of the universal physical factors of the environment is temperature. There is, perhaps, no other physical agent

the influence of which has been studied as extensively with both living and inanimate material. The present monograph deals with the effects of low temperature, and in particular is concerned with the following problems: 1, The lower limit of temperature for various forms of life; 2, physical state of protoplasm at low temperatures; 3, the mechanism of injury and death at low temperature.

A great deal of useful information has been brought together in this book; a fairly extensive bibliography directs the interested reader to original sources.

This book will be a welcome addition to the reference library of the general physiologist and pathologist.

B. L.

MEDICAL DISEASES OF WAR. By SIR ARTHUR HURST, M.A., D.M. (OXON.), F.R.C.P., Lieutenant-Colonel, Late R.A.M.C., Lecturer on Clinical Medicine, University of Oxford, and Consulting Physician to Guy's Hospital, etc. With the coöperation of H. W. BARBER, M.A., M.B. (CANTAB.), F.R.C.P., Physician-in-Charge of the Skin Department, Guy's Hospital, H. B. F. DIXON, M.C., M.D. (DUB.), D.T.M. and H., F.R.C.P., Lieutenant-Colonel (temporary Colonel), R.A.M.C., F. A. KNOTT, M.D. (LOND.), M.R.C.P., Bacteriologist to Guy's Hospital, T. A. ROSS, M.D. (EDIN.), F.R.C.P., Late Medical Director of Cassel Hospital for Functional Nervous Disorders, and ARNOLD W. STOTT, M.A. (CANTAB.), F.R.C.P., Colonel, R.A.M.C., Late Consulting Physician to the British Expeditionary Force; Physician to Westminster Hospital. Pp. 427; 48 illustrations. Second Edition. Baltimore: The Williams & Wilkins Company, 1941. Price, \$5.50.

First published in 1916 and again in 1918 under the title "Medical Diseases of the War," this volume has now reached its second edition during the present war, a testimony to its worth. Of particular value are the first 15 chapters, comprising more than a third of the book, on various aspects of psychoneuroses in service personnel. The detailed descriptions of etiology, symptoms, diagnosis and treatment, with many illustrative case reports, make this book most useful for all physicians, especially those in the armed forces. Other topics include: trench fever, typhoid and paratyphoid fevers, dysentery, epidemic jaundice, malaria, meningococcal fever, tetanus, digestive disorders in soldiers (the Reviewer is pleased to note the recognition of nervous tension as a factor in the etiology of peptic ulcer, previously denied by the senior author), war nephritis, effort syndrome, skin disease in war, gas poisoning (rather sketchy), and an index (not adequate). The book is highly recommended.

R. K.

CHINESE LESSONS TO WESTERN MEDICINE. A Contribution to Geographical Medicine from the Clinics of Peiping Union Medical College. By I. SNAPPER, M.D., Professor and Head of the Department of Medicine, Peiping Union Medical College, Peiping, China. With a Foreword by GEORGE R. MINOT, Professor of Medicine, Harvard University. Pp. 380; 132 illustrations and 38 tables. New York: Interscience Publishers, Inc., 1941. Price, \$5.50.

ONE of the fascinations of clinical medicine lies in the differences in disease pictures that result from variations in race, place and economic status: the geography of medicine. Studies in medical geography, in turn, broaden our concepts and understanding of these diseases. This volume offers many examples that are both interesting and instructive.

Since problems of nutrition are omnipresent in northern China, not only does the opening chapter deal with nutritional disorders, but the discussion of practically every disease mentioned in the book is colored by the nutritional factor. There are chapters on infectious diseases (including comparative strangers to western medicine, such as typhus, relapsing fever, kala-azar); tuberculosis; amyloid degeneration (rare in China, in spite of much tuberculosis and chronic bone suppuration); cardiovascular diseases (rheumatic fever clinically rare, but its late valvular evidences not uncommon; arteriosclerosis rare, blood pressures usually low); renal affections; diseases of the liver and biliary system (frequency of parasitic diseases and of portal cirrhosis without alcoholism; rarity of gall stones and occurring equally in both sexes); diseases of the blood-forming organs; malignant tumors (primary liver cancer common); intoxications (opium); miscellaneous diseases. Extremely well written, the book reflects the experiences of an excellent clinician and pays high tribute to the quality of medicine practised by his Chinese associates. The illustrations are numerous and well done. The subtitle might well be amended to read: "An excellent contribution to clinical medicine." Every physician will be a better doctor for having read this volume.

R. K.

SHOCK TREATMENT IN PSYCHIATRY. A Manual. By LUCIE JESSNER, M.D., PH.D., Resident Psychiatrist, Baldpate, Georgetown, Mass., Graduate Assistant in Psychiatry, Massachusetts General Hospital, Assistant in Psychiatry, Beth Israel Hospital, Boston, and V. GERARD RYAN, M.D., Associate Psychiatrist, Elmcrest Manor, Portland, Conn., Assistant in Psychiatry, Harvard Medical School. Introduction by HARRY C. SOLOMON, M.D., Clinical Professor of Psychiatry, Harvard Medical School, Chief of Therapeutic Research, Boston Psychopathic Hospital. Pp. 149. New York: Grune & Stratton, Inc., 1941. Price, \$3.50.

THIS manual deals with the use of insulin, metrazol and electric convulsive therapy in the treatment of the psychoses. It is brief, concise, and up-to-date. No attempt is made, as the authors say, to make it "a compendium nor does it purport to be a complete treatise on shock therapy." Almost all statements are supported by references to the current literature. Indeed, not the least valuable part of the volume is its extensive bibliography. Critics of the so-called shock therapies will find few arbitrary statements in this book. While it offers few new ideas to those experienced in these forms to therapy, it can heartily be recommended to anyone wishing an up-to-date short review of the subject.

T. R.

ENDOTRACHEAL ANESTHESIA. By NOEL A. GILLESPIE, D.M., B.Ch., M.A. (Oxon.), D.A. (R.C.S. Eng.), Research Associate and Resident in Anesthesia, University of Wisconsin General Hospital, etc. Pp. 187; 44 illustrations and 1 colored plate. Madison: The University of Wisconsin Press, 1941. Price, \$4.00.

THIS monograph is a compact, orderly and thorough presentation of the subject. Its author is well qualified for the task because of his wide personal experience and comprehensive grasp of the literature. Physiologic considerations are correctly combined with technical information and the book should be of interest to workers in the laboratory as well as to clinicians. The section on "blind intubation" is exceptionally well done. Here is a difficult procedure made easy by accuracy in observation and attention to

detail brought from experience in hundreds of cases. Entirely apart from factual data offered, the little volume repays study of its precision in selection of words and finesse of expression—a quality too often lacking in medical works today. The work can be unhesitatingly recommended to anesthesiologists, surgeons, bronchoscopists, and those who enjoy a job well done, whatever their special interest in medicine. R. D.

DENTAL MATERIA MEDICA, PHARMACOLOGY, AND THERAPEUTICS. By WALTER J. DILLING, M.B., CH.B. (ABERD.), M.P.S. (HON.), Professor of Pharmacology and General Therapeutics, School of Dental Surgery, Liverpool University, etc., and SAMUEL HALLAM, L.D.S., R.C.S. (ENG.), Honorary Dental Surgeon, Liverpool Royal Infirmary, etc. Pp. 348. Second Edition, revised. London: Cassell & Co., Ltd., 1941. Price, 13/6.

THIS book gives in concise form the pharmacologic actions of a large number of drugs, placing emphasis chiefly upon those used in dentistry. This book is compact, accurate and up-to-date, but because of the vast field covered in a small space, the authors often tend to be didactic and have omitted altogether references to original research work. J. C.

INDUSTRIAL SURGERY, Principles, Problems, and Practice. By WILLIS W. LASHER, M.D., Surgical Director, Employers Liability Assurance Corporation, New York; Assistant Professor, Traumatic Surgery, New York Post-Graduate Medical School. With a Foreword by CHARLES GORDON HEYD, M.D., Past-President of the American Medical Association. Pp. 472; 194 figures. Enlarged First Edition, 1942. New York: Paul B. Hoeber, Inc. Price, \$6.50.

THIS "enlarged edition" has all the merits of the first edition with the addition of two new chapters, one on sprains and strains and one on chemotherapy. The Reviewer would like to have seen the use of crystalline sulfanilamide recommended for use in all lacerated wounds rather than iodine or another antiseptic. While iodine is useful for skin antisepsis it is harmful when used within the wound. In the out-patient surgical service of civilian hospitals the sulfonamides have been found to be more effective in preventing infection than any other substance.

Industrial surgery today takes its place in importance in the war effort beside naval and army medicine and this book is a timely guide to all those engaged in industrial medicine. I. R.

SYNOPSIS OF APPLIED PATHOLOGICAL CHEMISTRY. By JEROME E. ANDES, M.S., Ph.D., M.D., F.A.C.P., Director of Department of Health and Medical Adviser, University of Arizona, Tucson; Formerly Assistant Professor of Pathology and Clinical Pathology, West Virginia University Medical School, and A. G. EATON, B.S., M.A., Ph.D., Assistant Professor of Physiology, Louisiana State University School of Medicine, New Orleans. Pp. 390. St. Louis: The C. V. Mosby Company, 1941.

IN this small book the authors have produced a potent distillate; it is all meat. The everyday facts about normal and abnormal human body chemistry that one wants to find in an almost pocket-sized ready reference are included with more than usual completeness; the necessary speculations are brief and concise.

The book is made up as follows: Part I, The Chemistry of the Blood, consists of 14 chapters (including a particularly good synopsis of the subject of acid-base balance in Chapter VI); Part II devotes 21 pages to the chemistry of the Cerebrospinal Fluid; and Parts III, IV and V deal with, respectively, Chemistry of the Urine, Functional Tests (renal, liver and endocrine), and Gastric Analysis and Basal Metabolism; an Appendix describes a number of reagents. Each chapter contains the well-established chemistry techniques for the estimation of each substance discussed, in adequate detail.

Each of the more important chapters contains a good table summarizing the variations found in health and disease and, what should be most useful to a practicing physician whose patient pays for individual chemistry tests but does not particularly desire to endow the laboratory; asterisks point out which tests are of emphatic clinical usefulness. Then there are two "master" tables covering blood chemistry in the first chapter of that section, where, under the heading Preliminary Considerations, there appears much pertinent advice about collection of specimens.

Although sulphonamide and other drugs do not come under the heading of normal or abnormal body metabolites, with which the subject of the book is concerned, the authors have wisely included a chapter "Tests for Drugs in the Urine" and the quantitative method for sulphanilamide in blood.

This book will appeal particularly to students of medicine (whether undergraduate or postgraduate) who are studying to pass examinations, to hospital internes and to clinical laboratory workers; and, no less, to practicing physicians who want on their desks for ready reference a handy-sized compendium of the facts of chemical physiology.

Several oversights of the proofreaders were noted: page 20, fourth line from bottom; page 65, third line from bottom; page 66, top line ("Normal values of urea are usually found in cardiac decompensation uncompensated by nephritis"); page 86, line 10 from top; page 278, line 13 from bottom; and on page 78, the first clause of the last sentence is an interesting way to put it. Aside from these inconsequential errors, this Reviewer noticed only one definite mistake: the definition of "volume index" on page 144, and its confusion with cell hemoglobin concentration or "saturation index."

D. B.

CLINICAL IMMUNOLOGY, BIOTHERAPY AND CHEMOTHERAPY in the Diagnosis, Prevention and Treatment of Disease. By JOHN A. KOLMER, M.S., M.D., DR.P.H., Sc.D., LL.D., L.H.D., F.A.C.P., Professor of Medicine, Temple University School of Medicine; Director of the Research Institute of Cutaneous Medicine; and LOUIS TUFT, M.D., Assistant Professor of Medicine and Chief of Clinic of Allergy and Applied Immunology, Temple University School of Medicine. Pp. 941, 27 illustrations. Philadelphia: W. B. Saunders Company, 1941. Price, \$10.00.

THIS volume represents a new departure in that it includes under the same cover a thorough presentation of the principles of infection, immunity, biotherapy and chemotherapy, and also a detailed discussion of the application of these principles in the diagnosis, prevention and treatment of specific diseases. Part I is devoted to the general aspects of the subject, with chapters on the mechanism of infection and the production of disease by living agents; natural and acquired immunity; antigens and antibodies, phagocytosis, the mechanism of antitoxic and antibacterial immunity; anaphylaxis and allergy; diagnostic immunologic reactions; active immunization and vaccine therapy; passive immunization and serum therapy; bacteriophage therapy; methods of diagnosis and treatment of allergy; blood transfusion therapy; non-specific protein therapy; chemotherapy. In Part II are discussed the various diseases produced by living agents and the

diseases due to allergy, with discussions of etiology, epidemiology and transmission, pathogenesis, immunology, diagnostic prophylactic and therapeutic measures. An interesting and useful feature of the book is found in the concise summaries at the end of each chapter or individual disease section, in the latter being tabulated and set apart in a box enclosure for easy reference. There are no detailed descriptions of serologic or purely laboratory methods; but the tests used by practicing physicians, such as diagnostic skin tests, are fully described. At the end of each chapter are given the principal references to the literature. Intended primarily for practitioners of medicine and public health, the book will also be useful to students and their teachers, both in the preclinical and clinical years. Both authors bring to their task a rich experience in investigation and practice in their respective fields. Questionable is an undue emphasis on biotherapeutic measures as opposed to chemotherapy, but the defect is of relatively minor importance. The work is highly recommended to physicians and students.

R. K.

NASAL SINUSES: An Anatomic and Clinical Consideration. By O. E. VAN ALYEA, M.D., Assistant Professor, Department of Laryngology, Rhinology, and Otolaryngology, University of Illinois College of Medicine, Chicago. Cloth. Pp. 270. Baltimore: The Williams & Wilkins Company, 1942. Price, \$6.50.

A NEW approach to the management of sinus abnormalities is presented by the author who feels that a correlation of anatomy and histopathology with the clinical picture of sinus disease will do much to clarify present therapeutic efforts. A bibliography appended to each chapter covers the literature since 1934. The illustrations are well chosen and succeed in demonstrating important anatomic features as well as showing therapeutic approaches.

H. S.

NEW BOOKS.

A Textbook of Clinical Parasitology Including Laboratory Identification and Technic. By DAVID L. BELDING, M.D., Professor of Bacteriology and Experimental Pathology, Boston University School of Medicine; Member of Staff of Evans Memorial and Massachusetts Memorial Hospitals, Pp. 890; 1500 illustrations. New York: D. Appleton-Century Company, Inc., 1942. Price, \$8.50.

Internal Medicine in Old Age. By ALBERT MUELLER-DEHAM, M.D., Associate Visiting Physician, Welfare Hospital for Chronic Diseases (Second Division), Department of Hospitals, New York City, etc. Pp. 377; 11 illustrations. Baltimore: The Williams & Wilkins Company, 1942. Price, \$5.00.

Psychosurgery—Intelligence, Emotion and Social Behavior Following Pre-frontal Lobotomy for Mental Disorders. By WALTER FREEMAN, M.D., Ph.D., F.A.C.P., Professor of Neurology, George Washington University, Washington, D. C., and JAMES W. WATTS, B.S., M.D., F.A.C.S., Associate Clinical Professor of Neurosurgery, George Washington University, Washington, D. C. With special psychometric and personality profile studies by THELMA HUNT, M.D., Ph.D., Associate Professor of Psychology, George Washington University, Washington, D. C. Pp. 337; 81 illustrations. Springfield, Ill.: Charles C Thomas, 1942. Price, \$6.00.

The History and Evolution of Surgical Instruments. By DR. C. J. S. THOMPSON (with a foreword by DR. CHAUNCEY D. LEAKE). Pp. 106; 115 illustrations. New York: Schuman's, 1942. Price, \$8.50.

Psychological Effects of War on Citizen and Soldier. By R. D. GILLESPIE, M.D., Physician for Psychological Medicine, Guy's Hospital, London. Pp. 250. New York: W. W. Norton & Co., Inc., 1942. Price, \$2.75.

- Nephritis.* By LEOPOLD LICHTWITZ, M.D., Chief of the Medical Division of the Montefiore Hospital; Clinical Professor of Medicine, Columbia University. Pp. 344; 120 illustrations. New York, Grune & Stratton, Inc., 1942. Price, \$5.50.
- Science and Man.* By RUTH NANDA ANSHEN. Pp. 494. New York: Harcourt, Brace & Co., 1942. Price, \$4.00.
- Rabies.* By LESLIE T. WEBSTER, M.D., The Rockefeller Institute for Medical Research, New York. Pp. 163. New York: The Macmillan Company, 1942. Price, \$1.75.
- The Medical Clinics of North America, Vol. 26, No. 2.* St. Louis. Pp. 635; 126 illustrations. Philadelphia, W. B. Saunders Company, 1942.

NEW EDITIONS.

- The Principal Nervous Pathways.* By ANDREW THEODORE RASMUSSEN, PH.D., Professor of Neurology, Department of Anatomy, University of Minnesota Medical School, Minneapolis, Minn. Pp. 65; 28 illustrations. Second Edition. New York: The Macmillan Company, 1941. Price, \$2.50.
- Endocrinology. Clinical Application and Treatment.* By AUGUST A. WERNER, M.D., F.A.C.P., Assistant Professor of Internal Medicine, St. Louis University School of Medicine, etc. Pp. 924; 327 illustrations. Second edition. Philadelphia: Lea & Febiger, 1942. Price, \$10.00.
- Hughes' Practice of Medicine.* Revised and Edited by BURGESS GORDON, M.D., Clinical Professor of Medicine, Jefferson Medical College; Director and Physician-in-Charge, Department of Diseases of the Chest, Jefferson Hospital, Philadelphia. Pp. 791; 36 illustrations. Sixteenth Edition Philadelphia: The Blakiston Company, 1942. Price, \$5.75.

"The book is intended primarily to present in concise form the clinical features and the treatment of disease. . . . As previously, theoretical and controversial views are not discussed as these are fully covered in the current literature, special monographs and the standard textbooks of medicine. . . . Among the new subjects are: focal infections; streptococcal, staphylococcal, *Bacillus pyocyaneus*, and *Bacillus proteus* infections; virus pneumonia; lymphogranuloma inguinale, epidemic pleurodynia; lymphocytic choreomeningitis, Pappataci fever; Tsutsugamushi disease; Blastomycosis, coccidioid granuloma; sporotrichosis; mycetoma; moniliasis; Balantidiasis; Coccidiosis; Sarcoidosis; erythema articum epidemicum; panniculitis; serum sickness; shock; electric shock; the effects of over-exposure to the x-rays; Marihuman (sic) habit; sulfonamide poisoning; war gas poisoning; mercury poisoning; arsenic poisoning; zinc poisoning, riboflavin deficiency; osteomalacia; tumors of the bone; hyperinsulinism; hemochromatosis; ochronosis; lipomatosis; regional ileitis; megacolon; tuberculosis of the intestine; affections of the mesentery; erythremia; hemorrhagic disease of the new-born; the cardiac neuroses; acrocyanosis; periarteritis nodosa; painful heel; frost bite; sinusitis; diseases of the ear; tuberculous tracheobronchitis; pulmonary infarction; lung injuries due to air raids; cysts of the lung; geriatrics; myasthenia gravis; amyotonia congenita; progressive muscular dystrophy; pseudo-hypertrophic muscular dystrophy; and family periodic paralysis." (Preface.)

- Diseases of the Skin.* By FRANK CROZER KNOWLES, M.D., Professor of Dermatology, Jefferson Medical College, etc., EDWARD F. CONSON, M.D., Clinical Professor of Dermatology, Jefferson Medical College, etc., and HENRY B. DECKER, M.D., Assistant Professor of Dermatology, Jefferson Medical College, Philadelphia. Pp. 621; 272 illustrations. Fourth Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1942. Price, \$7.00.

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PROGRESS OF MEDICAL SCIENCE

PEDIATRICS.

UNDER THE CHARGE OF
IRVING J. WOLMAN, M.D.

ASSOCIATE IN PEDIATRICS, UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE,
PHILADELPHIA, PA.

CYSTIC FIBROSIS OF THE PANCREAS.

WITHIN the past few years, out of the great catch-basket of chronic intestinal disorders comprised in the term "celiac disease," a new and significant entity has crystallized out. Though celiac disease itself was described by Gee²¹ in 1888, Herter's²⁹ monograph on intestinal infantilism emphasized to the medical profession the importance of the condition. In the early literature on celiac disease, one finds such prominent names as Gibbons,²² Bramwell,⁶ Cheadle,¹² Still,⁵⁰ Howland,³² Marriott,³⁸ Haas,²⁵ and Parsons.⁴³ There is general agreement now that these cases are not all alike and that several distinct pathologic processes may give rise to the clinical picture which Holt and McIntosh⁵¹ prefer to describe as the "celiac syndrome" rather than "celiac disease."

Passini⁴⁴ (1919) was apparently the first to describe an instance of faulty digestion in an infant due to pancreatic disease. Other reports soon followed, and it gradually became apparent that fibrotic lesions of the pancreas could give rise to symptoms of chronic intestinal indigestion resembling closely those which had been previously considered pathognomonic of celiac disease. Most cases of celiac disease, of course, fail to show any pancreatic changes, or for that matter, any pathologic lesions in any part of the gastro-intestinal tract. It remained for Parmelee⁴² in 1935 to indicate the probable relationship between infantile steatorrhea and deficiency of the pancreatic exocrine secretion. Harper²⁷ and Andersen^{2a} in 1938, and Ranch, Litvak and Steiner⁴⁶ in 1939, all working independently, threw this hitherto indefinite entity into sharp focus, reviewing the accumulated material in the literature, and correlating the available data with observations on personally observed cases. A number of additional important contributions have come forward in the past few years, and the pediatric profession has been made aware of the existence of the diagnostic possibility. Clinical recognition of cases is now of commonplace occurrence in many clinics, and progress has been made in the direction of successful treatment. For a complete historical review of the development of our modern concept of cystic fibrosis of the pancreas, the reader is referred to the above-mentioned key papers and that of Jeffrey.³¹

Frequency. General knowledge concerning this disorder is still too fresh for the securing of accurate data on its statistical frequency. Unless a microscopic examination is made of the pancreas of every infant coming to necropsy, whether stillborn or dying in the first few years of life, the existence of the lesions may escape recognition. Andersen's^{2a} original study comprised 49 cases, of which 20 were collected from the literature on celiac disease and pancreatic insufficiency, 7 from the literature on vitamin A deficiency, 2 from outside hospitals and 20 from the pathologic files of the Babies' Hospital, New York. Blackfan and May⁴ collected 35 examples in a review of 2800 postmortem examinations on children. Farber¹¹ stated he had seen this type of pancreas at autopsy in well over 40 cases in advanced form and in over 300 cases in minor degrees. Harper²⁸ reported 8 personally observed cases with postmortem observations on 5. Deem and McGeorge¹⁵ were able last year to make the clinical diagnosis on 7 infants having steatorrhea, confirming the diagnosis in the 1 case on which an autopsy was performed. They described 2 additional instances of congenital pancreatic fibrosis in infants dying in the neonatal period; in both infants the cause of death was congenital stenosis of the gut. Snelling and Erb⁴⁹ recognized 19 patients in a 20 year period, 14 of which were observed between 1937 and 1941. The most recent report, that of Jeffrey³⁴ refers to 88 cases from the literature and presents 2 new ones. Jeffrey and others have noticed a greater incidence in females (68%). The growing flood of papers on this topic will no doubt raise the total very much higher with the incidence of celiac disease regressing in inverse proportion.

Pathology. In most of the recorded instances no gross abnormalities of the pancreas have been detected although, to the experienced observer, the changes are often characteristic and readily recognized.^{2a,11} The gland may be narrower, much firmer in consistency and more pinkish-red than is normal for a child of this age, and occasionally a slight grating sound can be noted as a knife passes through calcified concretions. The lobules appear rounded and uneven in size. In the Reviewer's experience such affected glands have shown tiny opaque yellow foci scattered through their substance. Oppenheimer⁴¹ studied the findings in a 10 months' old white girl and found the pancreas normal in the fresh state, but after being fixed in Zenker's fluid numerous fine white opacities became evident. She was unable to demonstrate any opening of the pancreatic duct into the duodenum on gross dissection or on serial microscopic sections. After carefully going through the literature, Oppenheimer states that there are only 4 other cases recorded in which a congenitally occluded pancreatic duct appeared to be the initial lesion in cystic fibrosis of the pancreas. In most other cases the pancreatic duct was patent and in 1³⁷ it was dilated throughout.

On microscopic examination of the pancreas the ducts are distended, stenosed or atretic, and the acini and small ducts are dilated, containing inspissated coagulum or calcified concretions. The acinar cells may be flattened to form a thin epithelial wall about the coagula which are eosinophilic and sometimes laminated. Metaplasia of the epithelium of occasional ducts has been described. Surrounding the acini and also the lobules is an increased amount of fibrous tissue lightly or heavily infiltrated with mononuclear cells, lymphocytes and occasional

neutrophils. The islands of Langerhans are usually normal in size and number. In a few instances^{28,47} the acinar tissue was scanty or absent, being replaced by fat lobules. In association with these pancreatic changes one finds as a rule certain pulmonary changes present almost constantly at the time of death. These pulmonary changes consist of bronchitis, bronchiectasis, pulmonary abscesses arising in the bronchi, fibrosis or abscess of the lung, lobular pneumonia or any combination of these. *Staphylococcus aureus* is the predominant bacteriologic agent in most cases. Many but not all of the more recently studied cases have shown the keratinizing metaplasia of the bronchioles and other epithelial-lined organs which are characteristic of vitamin A deficiency.⁵ Fatty changes in the liver are usually present. The existence of congenital anomalies in other visceral organs has been repeatedly commented upon also. Keratomalacia resulting in corneal ulceration and opacities has been described in a few instances.^{5,10,19,53} There have been apparently no cases of keratomalacia occurring in celiac disease.

Etiology. The basic cause of this pancreatic disturbance has not been elucidated. In a few instances the appearances suggest fatty replacement of atrophied or undeveloped tissue. Blackfan and Wolbach⁵ suggest that the lesion has its beginning in a thickening of the physical character of acinar secretion; this material inspissates and causes obstruction with resulting hypofunction of the secretory mechanisms, initiating a progressive vicious circle. Andersen^{2a,b} points out that in some instances the changes in the pancreas appear to be the result of obstruction in the small or large pancreatic ducts and that the stenosis or atresia may have been the result rather than the cause of the fibrosis. Somewhat similar changes in the secretory tissue of the gland can be produced experimentally by surgical ligation of the pancreatic duct in animals. The high frequency of associated anomalies in these children, the fact that the changes may be well marked in infants dying in the first week of life, and the oft-noted familial incidence argue in favor of congenital malformation as the etiologic agent. On the other hand the fibrosis and cellular invasion suggest inflammation of the pancreas. There is no reason to incriminate congenital syphilis as the cause of this hypothetical inflammation. In the case of congenital obstruction of the intestine in the newborn the pancreatic change may be due to retrograde back pressure of secretion or possibly to ascending infection along the ducts. The presence in some cases of proliferation and metaplasia of the epithelium in the lungs and elsewhere throughout the body suggest the possibility of vitamin A deficiency in the mother before the child was born. This could explain the familial incidence in terms of deficiency of vitamin A in the maternal diet or of a disturbance in the mechanism of absorption of the vitamin in the mother. Unfortunately for this hypothesis attempts to reproduce the lesions experimentally in pregnant animals having congenital vitamin A deficiency has not been successful. Furthermore, it appears that in many children having this form of hypovitaminosis the duct epithelium of the pancreas fails to manifest the atrophy and metaplasia which becomes evident in other parts such as trachea, bronchial glands and renal pelvis.

Symptomatology and Clinical Course. Generally speaking, the cases can be divided into three groups: *a*, Those dying during the neonatal

period with symptoms of intestinal obstruction from inspissated meconium; *b*, those dying between the neonatal period and 6 months of age with failure to gain in weight; and, *c*, those dying after the sixth month with, in most instances, the celiac syndrome in addition to the clinical features typical of the second group.

The term "meconium ileus" describes intestinal obstruction in the newborn due to complete plugging of the intestinal lumen by a mass of thick gummy meconium. Dodd¹⁶ in 1936 reviewed the literature and found 21 instances. In 5 of these cases the child after showing symptoms of intestinal obstruction for several days passed one or more plugs of puttylike meconium and then was well. In the majority of other cases the child had no bowel movements, and the condition was diagnosed clinically as a congenital developmental obstruction of the gastrointestinal tract. At operation or at postmortem examination no other cause for the obstruction could be found. In most instances the intestine was enormously dilated above the meconium plug, and completely collapsed below. In several cases the intestinal musculature was hypertrophied at the point of obstruction. Rupture of the intestines with meconium peritonitis occurred in several children. As a rule, in these cases no lesions were found apart from changes in the pancreas, detectable microscopically. There was a marked increase in the fibrous stroma of the pancreas, accompanied by mild infiltration with phagocytes of various types. The acini were atrophic and scarred. The main pancreatic duct was dilated and thick-walled; the dilatation extended back into the duct branches and involved some of the acini. In 1 case the pancreatic duct was described as stenosed near its outlet.³⁶ This interesting though rare condition has not received much comment in the literature. Bronaugh and Lattiner⁸ recently described a typical case, and Adamson and Hild¹ have reported an unusual complication in the form of a secondary intussusception occurring during the prenatal period. Absence of pancreatic juice or, rarely, of bile results in inspissation of meconium with subsequent intestinal obstruction. There have been several cases^{18,37,52} in which obstruction to the passage of bile into the intestine was present and no pancreatic lesions. Most of the cases of meconium ileus have been operated on for intestinal obstruction, and the diagnosis not made until the abdomen is explored. One notes that some of the infants had been observed to pass a small quantity of thick puttylike material prior to operation, a finding which might give a clue to the true nature of the situation.

In the first months of life the child with cystic fibrosis of the pancreas has a good appetite and eats well, but fails to gain weight on an adequate diet. He usually has a number of pale, foul-smelling stools each day, often diarrheic in appearance. His general appearance is that of undernutrition, frailty and anemia, with prominence of the abdomen and general muscular hypotonia. On microscopic examination the stools contain large quantities of fatty material ("butter-stools"), visible grossly as well as microscopically. When the child is on unskimmed milk the fat in the feces may run from 40 % to 70 % of the dried material; a large proportion of the fecal fat remains unhydrolyzed, though this finding is not constant. Roentgenograms of the long bones usually show osteoporosis; rickets when present is usually mild. The infants have a low tolerance for alimentary fat including cod-liver oil and get

along much better on skimmed milk formulas. They sometimes develop keratomalacia or xerophthalmia, and are highly susceptible to respiratory tract infections. Many succumb during the infancy period to chronic interstitial bronchopneumonia complicated with bronchiectasis. That these patients have faulty absorption of vitamin A has been shown by Breese and McCoord,⁷ and by May and McCreary,⁴⁰ who showed a poor rise in the levels of vitamin A and of carotenoids in the blood following ingestion of large quantities of vitamin-rich fish-liver oil. In this regard the children react not unlike patients with celiac disease, except that their rate of absorption is very low, almost nonexistent. Apparently in pure celiac disease there is sufficient absorption over a prolonged period to account for the lack of vitamin A deficiency.

After the first 6 months of life the other manifestations of the celiac syndrome became apparent. Infantilism is striking, the muscles are wasted, the abdomen is large, meteorism is very prominent, the stools are bulky and malodorous, the glucose tolerance curve is flat, the gastro-intestinal roentgenograms show clumping, and the general picture shades into the familiar one originally described by Gee and Herter.

The problem of clinical diagnosis of cystic pancreatic fibrosis is being approached from the standpoint of assay of pancreatic enzymes in the duodenal secretion of patients suspected of having the disorder.^{2c} In pancreatic deficiency, and temporarily in marasmus, Andersen found that the values for trypsin, lipase and amylase were minimal, whereas in other gastro-intestinal conditions including celiac disease the values were in or near the normal range. The assay of trypsin was found to be most reliable, whereas that for amylase was inconstant and undependable. The next 12 months should see several additional reports from present workers in this field.

Differential Diagnosis. Because of the great overlapping in the clinical features, the differentiation from celiac disease is not always easy when the patient is beyond the stage of infancy when first seen. Generally speaking, with pancreatic fibrosis the onset occurs earlier and the clinical course is more severe. Anorexia is uncommon in the early stages. There are accompanying symptoms of bronchitis or low-grade lung involvement, and staphylococcal bronchopneumonia constantly threatens to carry the patient off. The level of vitamin A and of carotenoids in the blood is very low, and there is little or no response to the ingestion of a high test dose of fish-liver oil. In severe cases the patients do not respond well to the typical celiac disease diet, which is one high in protein, rich in carbohydrate and low in fat.

The most useful method for differentiating pancreatic steatorrhea from celiac disease would appear to be by studies on pancreatic secretion obtained by the duodenal intubation route, as discussed above. Analysis of the stools for the presence or absence of split fats has been suggested²⁵ as a means for differentiating between celiac disease and pancreatic fibrosis on the hypothesis that in the absence of pancreatic lipase the fat content of the stool would be in the form of triglycerides rather than in the form of fatty acids. This proposed differentiation point has not worked out in actual practice. In many cases of pancreatic fibrosis a high percentage of acids is found, the fats of the diet having been split presumably by lipase of the intestinal juice.¹⁵ Deem

and McGeorge have pointed out that the concentration of fat in the stool depends on the diet; on a low fat intake the stools may be normal but with a high fat diet the percentage of total fecal fat will rise.

Relation to Vitamin A Deficiency. Blackfan and Wolbach⁵ described a series of histologic changes in one or more parts of the respiratory system of 11 children who died with signs of vitamin A deficiency. These changes in brief consisted of bronchitis and pneumonia secondary to squamous metaplasia of the epithelium of the respiratory tract. This type of pneumonia was primarily an interstitial one with secondary involvement of the alveoli and the alveolar ducts. The bronchioles and small bronchi were greatly dilated, their lumens being filled with neutrophils. Their walls were thickened and surrounded by collections of phagocytes. Frequently destruction of the walls of the bronchioles occurred, and widespread replacement of living parenchyma by connective tissue was found in the more chronic cases. Bronchiectasis followed by interstitial invasion of the lung was the typical lesion. Interestingly, only 6 of their 11 cases showed cystic fibrosis of the pancreas. It is the general feeling that these bronchiectatic lung changes are either independent congenital anomalies occurring in association with a malformed pancreas, or else they represent the end-results of faulty vitamin A absorption from the intestinal tract. In favor of the vitamin A deficiency theory are reports on clinical improvement following feeding of large doses of vitamin A.^{2b,15,23} On the other hand some patients develop signs of bronchiectasis very early in life, before deficiency changes would be expected to appear,¹⁷ whereas many others fail to show any other positive evidences of hypovitaminosis clinically or pathologically.⁴⁶

Treatment. A few reports have appeared,^{2b,15,23} and the Reviewer knows of other instances, in which such children have been much helped by the use of pancreatin. Given in approximately 1 gm. doses, coincidentally with each bottle feeding, this crude pancreatic extract has produced resumption of weight gain, reduction in the quantity of fat lost in the stool, and an increase in the percentage of split fecal fat. In addition, the diet should be low in fat and high in calories, and vitamin A in generous quantities should be given both by mouth and parenterally. As Andersen^{2a,b} has pointed out, animals with ligated pancreatic ducts require greater quantities of food than normal to maintain health, and children having inadequate pancreatic function should similarly receive a caloric intake in excess of the usual amount for their age.

Terminology. Numerous names have been applied to this disease in the past, with the result that the nomenclature has been in a state of confusion. Cases in the literature have been reported as pancreatitis;³⁷ congenital stenosis of the pancreatic duct;³⁶ pancreatic disease;⁴⁴ atrophy of the pancreas;²⁴ congenital pancreatic steatorrhea;^{28,42} celiac disease;³⁰ congenital cystic fibromatosis of the pancreas;¹⁷ agenesis of exocrine portion of pancreas;⁴⁷ congenital pancreatic disease;¹¹ cirrhosis of the pancreas;²⁰ congenital familial steatorrhea.⁴⁶ In view of the obscurity which still attends the pathogenesis and fundamental nature of this interesting and puzzling lesion, it would seem wise, for the present at least, to continue with the currently popular term cystic fibrosis of the pancreas, which directs attention to two conspicuous features of the gross and microscopic findings.

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GYNECOLOGY AND OBSTETRICS.

UNDER THE CHARGE OF

CARL BACHMAN, M.D.

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

AND

FRANK B. BLOCK, M.D.

SURGEON, JEWISH HOSPITAL,
PHILADELPHIA, PA.

PHYSIOLOGY AND MECHANISM OF LABOR.

ADVANCES in our knowledge of the physiology and mechanism of labor have been made recently in a number of fields, more particularly in the domains of endocrinology, uterine motility and roentgenography.

Causes of the Onset of Labor. Danforth and Ivy⁴ recently have reviewed our understanding of this subject. The extrinsic nerves of the uterus appear to be entirely unnecessary for the spontaneous inception and maintenance of labor. Placentation, pregnancy and parturition may proceed unhindered after transection of the spinal cord, after lumbar sympathectomy, and following section of all of the extrinsic uterine nerves, or removal of the utero-vaginal ganglia. Whether the intrinsic uterine plexuses play a rôle is a debatable question, since they are necessary in some species, but apparently not in others.

Reynolds¹⁰ stresses the rôle of distention as a factor which inaugurates labor. He and others believe that there is no single known cause for the onset of labor; that parturition begins as the result of the gradual accelerating convergence of a number of factors—structural, humoral, nervous, nutritional and circulatory. These act at a time which is characteristic for each species, and, adapted to the morphologic conditions present in each, lead to the evacuation of the uterine contents.

He groups the factors controlling pregnancy and labor under two headings: 1, Those which stabilize pregnancy, and 2, those which stimulate the myometrium.

Stabilizing Factors. The two chief stabilizing factors are the corpus luteum and the placenta. Their relative importance varies in different species.

Corpus Luteum. Experiments indicate that any condition which prolongs the life of the corpus luteum, or which produces new corpora lutea has a tendency to prolong pregnancy, at least in certain species.

The rôle played by the corpus luteum shows species variations. This is illustrated by the observation that ovariectomy during pregnancy invariably results in abortion in such animals as the rat, mouse, rabbit, cow, squirrel, opossum and goat but not in man or the monkey. Intermediate between these two extreme effects of ovariectomy is the case of the guinea pig, in which ovariectomy after the first third of pregnancy does not always lead to abortion, although a high percentage of animals do abort, and those which do not usually produce small litters. The placenta is generally considered to be the source of these differences.

The Placenta. The existence of the placenta is believed to favor the maintenance of pregnancy. This is illustrated by the following experiment: If ovariectomy is performed upon animals, and all fetuses *but one* are removed, leaving all placental tissue *in situ*, the remaining fetus will survive, and the pregnancy will continue in a normal manner. Under these conditions the mass of placental tissue has been increased in proportion to the mass of fetal tissue. The placenta may either prolong the life of the corpus luteum, or take over its function by supplying a similar hormone.

Stimulating Factors. Estrin is believed to be necessary for the initiation and maintenance of coördinated rhythmic motility of the normal uterus. It increases its excitability, primes it for parturition, and increases its reactivity to the oxytocic principle of the posterior lobe of the pituitary gland. In the human, at least, estrin is believed to be elaborated by the placenta, as well as by the ovary, since ovariectomy does not modify the estrin excretion curve, yet, immediately after

parturition the estrin level drops to that observed in castrated women. One of the first effects of estrin upon the experimental animal is to produce hyperemia.

Certain clinical evidence suggests that estrin influences human uterine activity. For example, when given to amenorrheic women, it has stimulated tubal activity in what would be the mid-interval of the menstrual cycle. Also in young girls treated with estrin for gonorrheal vaginitis, low mid-abdominal cramps have been observed a day or two after the start of treatment. Furthermore, prolonged treatment with estrin has been observed to stimulate uterine activity in cases of missed abortion and uterine inertia.

The time interval between treatment and effect varies. During pregnancy, on the average, the latent period is about 7 hours; whereas, in the case of women treated some 7 days postpartum, it has been found to be as short as a few minutes.

Estrin is believed to bring about a progressive absorption of the amniotic fluid in late pregnancy. This effect appears at the time when the uterus is ceasing its most rapid growth. As a result of these changing conditions the fetus now occupies the place formerly filled by the fluid, and in part causes further distention of the uterus. The increasing distention tends to increase the irritability of the uterus. Also, since the fetus now has ceased to be a floating body, it is a better object for expulsion by the contracting uterine muscle. Experiments have shown that, in the case of the rabbit, the efficiency of the circulation of maternal blood through the placenta diminishes as pregnancy advances. This takes place at a time when the fetus is growing most rapidly, and is thought to result from the intra-uterine pressure.

In the human, at the start of the eighth lunar month of pregnancy, there has been observed a beginning thrombosis in many of the venous sinuses of the placenta, and the lumina of many of the vessels become obstructed with giant cells. Moreover, at this time the dry weight of the placenta increases less rapidly than does the volume of the placenta, whereas in the first 7 months of pregnancy the reverse holds true. The reversal of these two processes has been regarded as a sign of physiologic aging of the placenta. At this same time also, there is an increase in certain acids, especially amino-acids, and diminution of others such as proline, oxyproline, tryptophane, and especially arginine.

Certain observers have studied the placental content of acetylcholine and choline, but the results of their studies appear to be conflicting. Review of work on other hypothetical oxytocic substances leads to no final conclusions regarding the rôles which they might play in the mechanism of labor. For true labor, the heightened contractile powers of the uterus require the intermediation of integrating factors, for if intense contractions of the myometrium alone were sufficient for parturition, in the absence of an integrating factor, the administration of an oxytocic drug would hasten the process without real danger of rupturing the uterine wall.

What the factors are which coördinate the activity of the uterine muscle bundles during labor are not known. Although there is no evidence that the nerves to and within the uterus are essential for parturition, some observers, nevertheless, believe that an intrinsic nervous mechanism within the uterus is involved in the parturition mechanism,

and that the presence of sensorial corpuscles in the lower uterine segment offers anatomic support for this hypothesis.

Chemistry. Certain chemical changes occur in the uterus during pregnancy. These include a doubling in the amount of phosphocreatine, and paralleling this, a similar increase in its glycogen content. Both substances appear to be necessary for efficient muscular activity. In addition to these two substances, increases occur in glutathione and calcium.

Uterine activity and reactivity appear to be augmented by calcium ions and, conversely, are rendered relatively or absolutely quiescent by relative calcium lack. There also appears to be an interaction between calcium and potassium. Ivy has found that the absence of potassium may be just as potent a stimulus to the isolated uterus as an excess of calcium.

The female sex hormones appear to influence calcium metabolism. It has been demonstrated in recently parathyroidectomized animals maintained on minimal amounts of parathormone that tetany may be precipitated regularly by the occurrence of estrus, or pregnancy, or by the administration of extract of the anterior lobe of the pituitary gland, estrin or progestin. It thus appears that both estrogenic and progestational hormones are capable of diminishing the available calcium.

Uterine Contractions During Pregnancy and Labor. Murphy⁹ in a series of recent contributions has recorded the character of the uterine contractions which take place in women during pregnancy, in order to discover whether any correlation exists between prelabor and labor activity. He employed for this purpose the Lóránd tocograph, which is a simple mechanical device for registering the uterine contractions through the medium of the anterior abdominal wall. On the basis of more than 1800 separate observations, he records the following: He made his earliest tracing on the 110th day of gestation.^{9a} Although fetal movement was recorded as early as the 130th day, spontaneous uterine contractions were not registered until the 166th day of pregnancy. The first recordable increase in general uterine tonus did not appear until the 222d day of gestation.

The character of the uterine movements was influenced by the progress of pregnancy in the following manner: In the earlier months the uterus exhibited very little spontaneous activity. In some instances for more than 1 hour the uterus exhibited no spontaneous activity. This was followed by increasing activity which was rather slight in amount until a month or so before the onset of labor. This early activity was characterized by non-rhythmic contractions exhibiting great variability. Several weeks before the onset of clinical labor, non-rhythmic variable activity was supplanted by rhythmic activity which persisted until clinical labor began.^{11b} During this last period, although the duration and strength of the contractions increased greatly, there was but little if any change in their frequency.

Throughout both pregnancy and labor, although the pattern of contraction varied from patient to patient, there was observed an unusual similarity in the contraction patterns of any given individual from day to day. The character of the uterine activity during pregnancy gave some clue to what the labor might be like. For example patients who experienced spontaneous contractions prior to the

week of gestation, had significantly shorter labors than those women who did not exhibit such early activity.^{11a} Likewise, multigravidas and patients experiencing relatively short labors exhibited contractions during late pregnancy which were less frequent, more rhythmic in occurrence, stronger and longer in duration than did primigravidas and individuals who had longer labors.^{11c}

From the sixth lunar month onward there occurred a progressive increase in the amount of spontaneous activity, which was accompanied by a similar increase in the degree of responsiveness of the uterus to the administration of oxytocic drugs^{9d}. There also appeared to exist a correlation between the contractile response of the uterus to posterior pituitary extract during the last two months of pregnancy, and the character of the labor as indicated by its length.^{11e} Patients who reacted to posterior pituitary extract experienced shorter labors than those who failed to react. Of the women who reacted, those who experienced a clonic reaction had shorter labors than those who experienced a tetanic form of reaction.

Anatomy of the Human Pelvis. Two classifications of the bony female pelvis have been formulated recently which are an aid to a better understanding of the mechanism of labor, and are of assistance in the management of patients who present difficulties during delivery. These classifications have been arrived at from a study of skeletal material and also from roentgenography of the living individual.

Thoms Classification. According to this classification¹¹ female pelves fall into four major groups:

Class I. *Dolichopellic (Anthropoid)*. In this group the antero-posterior diameter of the pelvic inlet exceeds its transverse diameter, the pelvis being elongated antero-posteriorly.

Class II. *Mesatipellic (Round Type)*. Here the antero-posterior and transverse diameters are of equal length, or the transverse exceeds the antero-posterior by more than 1 cm. and less than 3 cm.

Class III. *Brachypellic (Oval Type)*. The transverse diameter is more than 1 cm. and less than 3 cm. greater than the antero-posterior diameter.

Class IV. *Platypellic (Flat Type)*. The transverse diameter exceeds the antero-posterior by 3 cm. or more.

Caldwell and Moloy Classification. Here the pelves are classified in four major groups, but with numerous subgroups.¹ The major groups are as follows:

Class I. *Gynecoid*. This is the normal pelvis of other classifications.

Class II. *Android*. The inlet of this pelvis is triangular in shape.

Class III. *Anthropoid*. The inlet is oval with its longest diameter antero-posterior.

Class IV. *Platypelloid*. The inlet is oval with its longest diameter transverse.

In addition to the shape of the inlet, other features are taken into account such as the size of the sacrospinous notch and the nature of the angle formed by the pubic arch.

Although study of pelvic configurations has thrown considerable light upon pelvic architecture, as yet there appears to be no agreement as to which of the two above classifications is the more practical. All observers admit, however, that knowledge of pelvic type facilitates a more

careful selection of patients for Cesarean section before labor, and that it is an aid in the conduct of difficult labors.

Relation Between Pelvic Type and General Physical Characters. Ince,⁷ from a study of 500 patients, could find no correlation between the type of pelvis and the general physical character of the individual, as expressed in her type of body build. Likewise he could find no correlation between such things as the male distribution of body hair, and the so-called male tendencies in the configuration of the female pelvis.

Pelvic and Fetal Measurements. Studies in Roentgen pelvimetry indicate that the commonly employed manual measurements of the pelvis, especially that of the external conjugate, are of relatively little value. For example, Dippel,⁶ from a study of 115 pelves, discovered that the difference between the external conjugate, and the obstetric conjugate, ranges from 4.93 to 13.5 cm. Consequently, he considers that the external conjugate measurement not only is useless but may be misleading, and therefore might as well be discarded as an obstetric procedure. Judson⁸ holds similar views.

Dippel, likewise, compared the diagonal and obstetrical conjugates. He found that a diagonal conjugate of 10.5 cm. might be associated in one case with an obstetrical conjugate of 10.2 cm. and in another instance with one of 8.2 cm. He concluded that Roentgen ray pelvimetry is unnecessary, however, when the diagonal conjugate is 11.5 cm. or more, but necessary when less than 11.5 cm.

Judson⁸ finds no correlation between fetal weight and headsize as measured before birth.

Position of Head on Engagement. In the past it has been held that the sagittal suture of the head enters the pelvic inlet most often in one of the oblique diameters. Current Roentgen studies^{2b} indicate that such is not the case; that the head enters most often in the transverse diameter of the inlet.

Why the occiput enters the posterior pelvis in one instance, and the anterior in another, has never been determined. Judson⁸ studied the pelves of 325 unselected primiparas roentgenographically, and concluded that the occurrence of occiput posterior positions bears no relation either to the shape of the pelvic inlet or to its size. On the other hand, Caldwell and Moloy and Thoms find that the occiput posterior position is associated frequently with pelves that have a relatively long antero-posterior diameter. This observation has the support of other workers.

D'Esopo⁵ finds that the position of the head on engagement depends, not only on the relative length of the antero-posterior diameter *versus* the transverse diameter of the pelvic inlet, but also upon the degree of narrowing of the forepart of the pelvic inlet. He observes that the narrower the pelvic brim as a whole, the more anteriorly or posteriorly will the fetal occiput lie.

Mode of Engagement of the Head. Caldwell and Moloy^{2b} have given us a new interpretation of the manner in which the head engages. Previously it was held that lateral flexion of the head tended to bring it synclitic with the inlet, *i. e.*, the biparietal diameter becomes parallel to some diameter of the plane of the pelvic inlet.

From Roentgen ray studies the above mechanism does not appear to be the usual procedure. According to Caldwell and Moloy the head engages in a posterior parietal presentation, with the sagittal suture

directed toward the symphysis. The anterior parietal bone slips behind the symphysis, while the posterior parietal bone remains relatively stationary. Thus the condition of synclitism rarely develops.

Flexion. In the past, the attitude of the fetal head called flexion, *i. e.*, the apposition of the chin to the chest, has been explained on the ground that the distance from the foramen magnum to the chin is longer than the distance to the occipital protuberance, and in accordance with the law of the lever, the long arm will ascend when the head meets resistance.

D'Esopo⁵ explains flexion not on this reasoning but on the relationship between the line of force in the direction of the fetal spine and foramen magnum to the occipito-frontal plane. He believes that this is the best explanation since it permits of varying lengths of lever arms, depending upon the angle at which the force transmitted through the axis of the fetal spine is directed at the occipito-frontal plane.

Rôle Played by Soft Parts. Caldwell, Moloy and D'Esopo^{2a} have studied the relation between the presenting part and the pelvis at various levels during the course of labor, and make interesting observations regarding the rôle played by the soft parts.

They find that the lower uterine segment and its fascial attachments influence the feto-pelvic relationship throughout labor. Even before the head impinges upon the pelvic inlet they have noted definite moulding of the skull bones suggesting that muscular activity is responsible for this, as well as the fitting of the head into the pelvic brim.

Caldwell and Moloy observed that the lower uterine segment and its fascial attachments exhibit their maximum guiding influence only after definite dilatation of the cervix has occurred. During labor the lower uterine segment normally causes the head to travel through the posterior segment of the pelvis, and at the same time produces flexion and moulding. The head may descend, however, through the anterior part of the pelvis; here it encounters more resistance which often leads to slow dilatation of the cervix and inertia. It is apparently impossible, before the onset of labor, to determine in which part of the pelvis the head will descend. Numerous roentgenographic studies indicate that the axis of the lower uterine segment does not always coincide with the optimum axis of the pelvic canal. The head may enter the fore pelvis, rather than the posterior segment, and as labor progresses, it may shift, due to the influence of the soft parts. Errors in the mechanism produced by the action of the soft parts may result in serious dystocia.

Internal Rotation. Current textbooks state that the head rotates internally as a result of meeting the resistance of the inclined plane of the pelvic floor, and whatever part of the infant reaches this first rotates to the front. D'Esopo⁵ finds that the internal rotation receives its directional force first of all from variable resistances offered to it by the bony pelvis, in all of the pelvic planes through which the head descends, and only finally from the inclined planes of the pelvic floor. He observes that the internal rotation is influenced primarily by the shape of the pelvis.

Danforth, Graham and Ivy³ studied the functional anatomy of labor as revealed by frozen sagittal sections of the *Macacus rhesus* monkey. They found the first stage of labor to be characterized chiefly by retraction of the isthmus uteri. The intrinsic dimensions of the cervix did not alter appreciably during this period.

During the second stage of labor the cervix retracted to or above the true conjugate, and was accompanied by elongation of the vaginal portion of the birth canal. The corpus and isthmus retracted at a similar rate during the early part of the second stage. The shortening of the isthmus occurred early in labor and was sustained until it relaxed to receive the placenta. In contrast to the isthmus, the corpus maintained its shortening or brachystasis, which became even more marked after the birth of a part of the fetus. The isthmus did not lengthen in the absence of disproportion, but was relatively thin in contrast to the corpus. The placenta became almost completely separated by the end of the second stage of labor.

DOUGLAS P. MURPHY, M.D.

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PHYSIOLOGY.

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SESSION OF APRIL 21, 1942.

The Electrical Potential of Acetylcholine and Choline in "Oil" Cells.

R. BEUTNER and T. C. BARNES (Department of Pharmacology, Hahnemann Medical College). Our communication is concerned with the one fact that acetylcholine is extremely active in "oil" cells. The type of "oil" cell used is a cup, filled with nitrobenzene or another "oil," immersed in a saline solution containing benzoate. The addition of acetylcholine even in dilutions of 1:100,000,000 negativates perceptibly the potential difference at the junction of "oil" and water. Since various water-immiscible substances in contact with saline are influenced by acetylcholine addition, one must conclude that the acetylcholine formed at the surface of the lipoid nerve fiber, also produces a negative electromotive variation which is probably the spike potential. Therefore, there is no contradiction between the chemical and electrical theories of nerve transmission.

There is a distinct specificity of action on these phase boundaries in "oil" cells: *acetylcholine* will produce negativity on nitrobenzene, guaiacol, and probably on some of the sterols but fails to work on glycerides like triacetin. *Epinephrine* produces a marked electrical

effect on triacetin, representative of glyceride fats. We can thus understand the difference in action of acetylcholine and epinephrine-like hormones on cholinergic and on adrenergic nerves.

Difficulty arises from the well-known theory which assumes that bioelectric potential differences arise through the filtration of ions in electrically charged pores. This theory remains a hypothesis which has never been confirmed, in spite of countless attempts, including the experiments on collodion membranes by L. Michaelis. The explanation of biological currents and potential differences must be based on facts and *not* on flimsy hypotheses.

Extracellular Fluid Volume in Man, Its Measurement and Relation to Season. ARNOLDUS GOUDSMIT and LAWRENCE LOUIS (Department of Physiology, University of Pennsylvania). Extracellular fluid volume (E.F.V.) was determined in healthy male volunteers as the mass of the water over which bromide and thiocyanate are distributed after their intravenous injections ("bromide space" [B.S.] and "thiocyanate space" [T.S.]). Final volume of distribution is not reached until 12 hours. Thirty minutes and 90 minutes after the injection the volumes are only 82.9% and 90% of their final volumes, respectively. T.S. amounts to 88.1% of the B.S.; the final B.S. to $29.2 \pm 2.4\%$ of the body weight (B.W.).

In these normal individuals an inverse relationship was found to exist between serum proteins and E.F.V., a decrease of 1 gm. of protein being correlated with an increase of $3.8 \pm 0.8\%$ (of the B.W.) in the E.F.V. Using such a correction, final B.S. was found to be $29.2 \pm 1.8\%$ of the B.W.

These fluid spaces are well reproducible in a given individual; the standard deviation from the mean of repeated determinations was $\pm 1.2\%$ of the total E.F.V. Repeated determinations were made on 7 individuals between October, 1940, and July, 1941, while outside temperatures varied between 16° and 95° F. Total E.F.V. (viz., circulating blood volume plus so-called "interstitial fluid") was found to remain essentially constant throughout the period. Thus, inasmuch as there is a definite increase of the circulating blood volume in the warmth, the changes with season tentatively may be tabulated as follows:

	Season.	
	Cold.	Warm.
	% of body weight.	% of body weight.
Interstitial fluids	20	18½
Blood volume	9	10½
Total extracellular fluids	29	29

Part, if not nearly all, of these shifts may well take place in the skin.

Reactions of Peripheral Vessels of Rabbits in Hypertension and in Response to Injections of Angiotonin. RICHARD G. ABELL and IRVINE

H. PAGE (Department of Anatomy, University of Pennsylvania, and Lilly Laboratory for Clinical Research, Indianapolis City Hospital). Living arterioles in transparent moat chambers (Abell, R. G., and Clark, E. R.: *Anat. Rec.*, **53**, 121, 1932) in the ears of normotensive rabbits were observed with the microscope, and their diameters measured. The animals were then made hypertensive by the methods of Goldblatt (Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: *J. Exp. Med.*, **59**, 347, 1934) and of Page (Page, I. H.: *Science*, **89**, 273, 1939), and the diameters of the same arterioles measured again.

Of the 10 rabbits operated upon, 4 became hypertensive. The blood pressure rose to from 1.4 to 2.1 times the normal level. Upon development of hypertension, persistent arteriolar constriction to from approximately 0.4 to 0.7 their control diameters occurred in all instances. This constriction did not interrupt the blood supply, but presumably did increase the resistance to blood flow. No such persistent constriction was observed in the rabbits that did not become hypertensive.

No capillary constriction was observed in the hypertensive rabbits; a slight constriction of some of the larger venules may have occurred.

Persistent hypertension was associated in 2 instances with a few small hemorrhages. During the development of hypertension and its continuance for a few days, new arteriovenous anastomoses appeared in the chambers.

Intravenous injection of angiotonin into normotensive rabbits caused arteriolar constriction of approximately the same degree as occurred upon the subsequent development of persistent hypertension.

In preliminary microscopic observations on vessels studied in a loop of intestine and its mesentery exteriorized in a celluloid chamber after the method of Zintel (Zintel, H. A.: *Anat. Rec.*, **66**, 437, 1936), angiotonin, injected intravenously, produced a similar partial constriction of the mesenteric arterioles in a normotensive rabbit.

Transplantation of Aneurogenic Forelimbs in *Amblystoma Punctatum*. JEAN PIATT (Department of Anatomy, University of Pennsylvania). Normal peripheral nerve distribution is attained by virtue of the early and intimate contact between nerve and end organ anlage during embryonic development. The question arises whether a normal nerve pattern may also result when morphogenesis occurs prior to nerve outgrowth.

Operations were performed in three steps: (1) Extirpation of spinal cord segments 2-6 inclusive at stages 23-25; (2) parabiosis of operated embryo with normal of same stage; (3) grafting of aneurogenic right forelimb of operated member of pair in place of corresponding limb of normal larva of same age, 10 to 14 days postfeeding. Grafted limbs were allowed to grow until the host animals were approaching metamorphosis.

Limbs were studied with regard to initiation and development of function, after which the animals were killed and the normalcy of the nerve pattern determined.

All limbs attained the power of completely individuated movement and each functioned in coordination with the contralateral host fore-

limb. This occurred in some cases as early as fifteen days following limb transplantation. Innervation of specific muscles was approximately normal; so-called normal innervation itself is subject to wide variation. The general nerve pattern was diagnostic of the typical punctatum forelimb and normal in most major particulars. Certain abnormalities occurred with greater frequency than others. The necessary conclusion from these experiments is that normal peripheral nerve distribution can be implemented by factors other than those operative in early ontogeny.

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